

Specification

Novel 2-heteroaryl substituted benzimidazole derivative.

The Field of Technology

This invention relates to the following, namely, glucokinase activator containing as effective ingredient 2-heteroaryl substituted benzimidazole, which is useful in field of medicine. Furthermore, it relates to a novel 2-heteroaryl substituted benzimidazole derivative.

Background technique.

Glucokinase (GK) (ATP : D-hexose 6-phosphotransferase, EC2.7.1.1) is one of the 4 types of kinases of mammals (hexokinase IV). The hexokinase is the enzyme of the first step of the glycolytic pathway and catalyses the reaction from glucose to glucose-6-phosphate. The expression of glucokinase is mainly localised in liver and pancreatic β cells, and plays an important role in the glucose metabolism of the whole body by controlling the rate limiting step of the glucose metabolism of these cells. The glucokinases from liver and pancreatic β cells have different sequences of the N-terminal 15 amino acids due to difference in splicing, however, enzymatic characteristics are the same. In three hexokinases (I, II and III) other than glucokinase, the enzyme activity reaches saturation at glucose concentration of 1 mM or less, whereas the K_m of glucokinase with respect to glucose is 8 mM which is close to the physiological blood sugar value. Accordingly, in the form of responding to the blood sugar change from normal blood sugar (5 mM) to elevated blood sugar after meals (10-15 mM), facilitation of intracellular glucose metabolism takes place via glucokinase.

A hypothesis has been proposed from about 10 years ago, wherein the glucokinase acts as the glucose sensor of liver and pancreatic β cells [cf. for example, Garfinkel et al., Computer modeling identifies glucokinase as glucose sensor of pancreatic β -cells, American journal Physiology), Vol. 247 (3Pt2), 1984, pp. 527-536].

It is becoming clear from the recent results of glucokinase gene manipulation mice that in fact, the glucokinase plays an important role in the glucose homeostasis of whole body. The mouse in which glucokinase gene has been destroyed dies shortly after birth [cf. for example. Transgenic Knockouts reveal a critical requirement for pancreatic β -cell glucokinase in maintaining glucose homeostasis, Cell, Vol. 83, 1995, pp. 69-78], on the other hand, in the normal and diabetes mellitus mice that overexpressed glucokinase, the blood glucose level becomes low [cf. for example. Ferre T, et al. Correction of diabetic alterations by glucokinase, Proceedings of the National Academy of Sciences of the U.S.A., Vol. 93, 1996, pp. 7225-7230].

As a result of increase in the glucose concentration, although the reactions of the liver and the

pancreatic β cell differ, both responds in the direction of lowering the blood sugar. The pancreatic β cell starts to secrete more insulin, and the liver takes in sugar and stores as glycogen and at the same time, lowers the sugar release.

In this way, the fluctuation of glucokinase enzyme activity plays an important role in glucose homeostasis of mammals through liver and pancreatic β cell. In the cases that develop diabetes mellitus in youth, called MODY2 (maturity-onset diabetes of the young), a mutation in glucokinase gene is discovered, and the lowered activity of glucokinase becomes the cause of blood sugar elevation [cf. for example, Vionnet N. et al., nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus, *Nature Genetics*, Vol. 356, 1992, pp. 721-722].

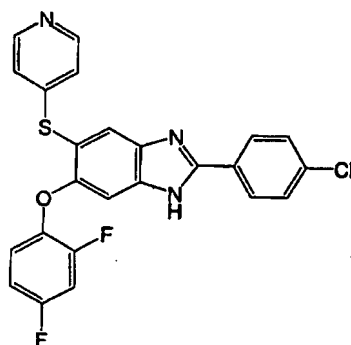
On the other hand, the lineage having mutation that increases glucokinase activity is also found, and such persons display hypoglycemic symptoms (cf. for example, Glaser B, et al, Familial hyperinsulinism caused by an activating glucokinase mutation, *New England Journal Medicine*, Vol. 338, 1998, pp. 226-230].

From these, glucokinase also functions as glucose sensor in human and plays an important role in glucose homeostasis. On the other hand, blood glucose control using glucokinase sensor system is regarded as possible in many type II diabetics. Because the glucokinase activator can be expected to have insulin secretion facilitation action of pancreatic β cell and sugar up take facilitation and sugar release suppression action by the liver, it is considered as useful as therapeutic drug for the type II diabetes mellitus patients.

Recently, it became clear recently that pancreatic β cell type glucokinase was expressed in rat brain, in particular, located in the feeding centre (Ventromedial hypothalamus, VMH). About 20% of VMH is called glucose responsive neurons, and has been considered from the past to play an important role in body weight control. When glucose is administered to rat brain, the food consumption falls, whereas, when the glucose metabolism is suppressed by intracerebral administration of glucosamine, an glucose analogue, overfeeding is observed. From electrophysiological experiments, the glucose responsive neurons are activated in response to physiological glucose concentration change (5-20 mM), however, when the glucose metabolism is suppressed with glucosamine or the like, activity suppression is observed. As the glucose concentration detection system of VHM, a mechanism via glucokinase similar to the insulin secretion of pancreatic β cell is assumed. Accordingly, a substance that activates the glucokinase of VHM in addition to liver and pancreatic β cell has a potential to correct obesity that becomes a problem in may type II diabetic mellitus patients as well as the blood sugar correction effect.

From the above description, the compound having glucokinase activation action is useful as therapeutic agent and/or preventive agent of diabetes mellitus, or as therapeutic agent and/or preventive agent of chronic complication of diabetes mellitus such as retinopathy, nephropathy, neurosis, ischemic cardiac disease, arteriosclerosis or the like, and moreover as therapeutic agent and/or preventive agent of obesity.

As far as benzimidazole derivative is concerned, for example, compounds represented by following formula

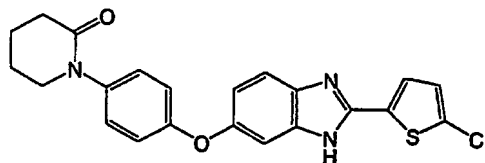


have been described (cf. for example Kokai 2000-026430).

Although the compound described by the aforesaid formula has a substituent at the 2 position of benzimidazole skeleton, the substituent thereof is 4-chlorophenyl and it is different from the A ring in accordance with this invention.

Moreover, the application of the said compound relates to interleukin production suppression, and there is no description that the said compound is useful for the therapy and/or prevention of diabetes mellitus, nor, there is a description suggesting this.

Moreover, as far as benzimidazole derivative is concerned, for example, compounds represented by following formula



are described (cf, for example, W O2004-017963).

The compound described by the aforesaid formula contains only one substituent on benzene ring of the benzimidazole skeleton, moreover although it has a substituent in 2 position of the benzimidazole skeleton, the substituent thereof is 5-chlorothiophenyl, and it is different from the A
©Rising Sun Communications Ltd. <http://www.risingsun.co.uk>

ring in accordance with this invention.

Moreover, the application of the said compound relates to Factor Xa and Factor VIIa inhibitors, and there is no description that the said compound is useful for the therapy and/or prevention of diabetes mellitus, nor, there is a description suggesting this.

Disclosure of the invention.

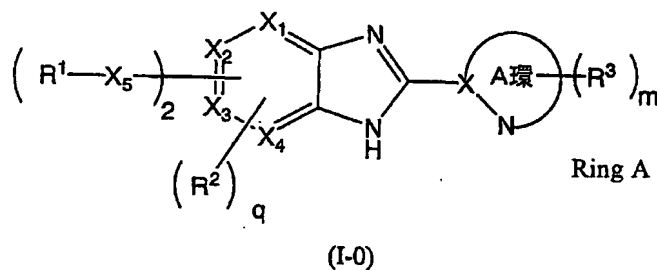
Problems to be overcome by this Invention.

The object of this invention is to put forward novel 2-heteroaryl substituted imidazole derivative and glucokinase activator using this and in particular to put forward a therapeutic agent and/or preventive agent of diabetes mellitus and obesity.

These inventors carried out assiduous investigation in order to develop a novel diabetes mellitus drug which has drug efficacy exceeding the preexisting diabetes mellitus drug due to different action from aforesaid preexisting drugs, and a novel diabetes mellitus drug having new efficacy, as a result, the novel 2-heteroaryl substituted benzimidazole derivative has glucokinase activation action. This invention was completed based on this discovery.

Namely, this invention relates to the following:

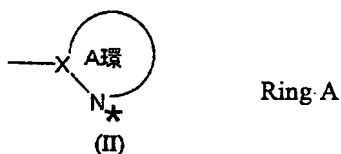
(1) A compound represented by Formula (I-0), or pharmacologically acceptable salts thereof



(wherein, X denotes a carbon atom or nitrogen atom,

X₁, X₂, X₃ and X₄ each independently denote carbon atom or nitrogen atom,

A ring denotes a 5-6 membered nitrogen containing heteroaromatic ring represented by formula (II)



which may containing 1-3 heteroatoms selected from nitrogen atom, sulfur atom and oxygen

atom in the ring (excluding the nitrogen atom represented by N* in formula II), or a bicyclic ring in which the said nitrogen containing heteroaromatic ring and phenyl or pyridyl are condensed, R¹ denotes aryl or a 4-10 membered monocyclic or bicyclic heterorings containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said R¹ may be each independently substituted with 1 to 3 R⁴, moreover, when the said heteroring is an aliphatic heteroring, it may contain 1 or 2 double bonds),

R² each independently denote hydroxy, formyl, -CH_{3-a}F_a, -OCH_{3-a}F_a, amino, CN, halogen, C₁₋₆ alkyl or (CH₂)₁₋₄OH,

R³ denotes -C₁₋₆ alkyl, -(CH₂)₁₋₆-OH, -C(O)-OC₁₋₆ alkyl, -(CH₂)₁₋₆-OC₁₋₆ alkyl, -(CH₂)₁₋₆-NH₂, cyano, -C(O)-C₁₋₆ alkyl, halogen, -C₂₋₆alkenyl, -OC₁₋₆alkyl, -COOH, -OH or oxo,

R⁴ each independently,

-C₁₋₆ alkyl (the said alkyl may be substituted with the same or different 1 to 3 hydroxy, halogen, -OC(O)-C₁₋₆ alkyl (the said alkyl may be substituted with 1 to 3 halogen), or -OC₁₋₆ alkyl)

-C₃₋₇ cycloalkyl,

-C₂₋₆ alkenyl,

-C(O)-N(R⁵¹)R⁵²,

-S(O)₂-N(R⁵¹)R⁵²,

-O-C₁₋₆ alkyl (the said C₁₋₆ alkyl may be substituted with halogen or N(R⁵¹)R⁵²),

-S(O)₀₋₂-C₁₋₆ alkyl,

-C(O)-C₁₋₆ alkyl (the said C₁₋₆ alkyl may be substituted with halogen, amino, CN, hydroxy, -O-C₁₋₆ alkyl, -CH_{3-a}F_a, -OC(O)-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)C(O)O-C₁₋₆ alkyl, -NH-C(O)O-C₁₋₆ alkyl, phenyl, -N(R⁵¹)R⁵²-NH-C(O)-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)-C(O)-C₁₋₆ alkyl or -NH-S(O)₀₋₂-C₁₋₆ alkyl),

-C(S)-C₃₋₇ cycloalkyl,

-C(S)-C₁₋₆ alkyl,

-C(O)-O-C₁₋₆ alkyl,

-(CH₂)₀₋₄-N(R⁵³)-C(O)-R⁵⁴,

-N(R⁵³)-C(O)-O-R⁵⁴,

-C(O)-aryl (the said aryl may be substituted with halogen),

-C(O)-heteroaromatic ring,

-C(O)-aliphatic hetero ring,

hetero ring (the said hetero ring may be substituted with -C₁₋₆ alkyl (the said -C₁₋₆ alkyl may be substituted with halogen or -O-C₁₋₆ alkyl),

phenyl (the said phenyl may be substituted with halogen, -C₁₋₆ alkyl, -O-C₁₋₆ alkyl),

halogen, CN, formyl, COOH, amino, oxo, hydroxy, hydroxy amidino or nitro,

R⁵¹ and R⁵² each independently denote hydrogen atom, -C₁₋₆ alkyl,

or 4-7 membered hetero ring formed by linking nitrogen atom, R⁵¹ and R⁵² together,

R⁵³ denotes a hydrogen atom or -C₁₋₆ alkyl,

R^{54} denotes $-C_{1-6}$ alkyl or,

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R^{53} and R^{54} , and $-N-C(O)-$ together or

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R^{53} and R^{54} , and $-N-C(O)-O-$ together (the said aliphatic hetero ring may be substituted with oxo, and moreover, the said aliphatic hetero ring may contain 1 or 2 double bonds in the ring),

X_5 denotes $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, single bond or $-O-C_{1-6}$ -alkyl",

a denotes, each independently, an integer of 1, 2 or 3,

q denotes an integer of 0-2,

m denotes an integer of 0-2]

(wherein the following cases were excluded:

the case wherein one of X_5 is $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$, and the other X_5 is single bond, and also

R^1 is aryl or nitrogen-containing aromatic heteroring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said aryl may be substituted with 1-3 R^4),

the case wherein both X^5 are single bonds, or

the case wherein both R^1 are aliphatic heteroring).

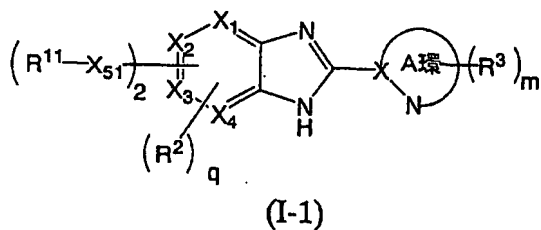
Moreover, this invention also relates to the following:

(2) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein in formula (I-0), X_1 to X_4 are all carbon atoms, or

(3) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein in formula (I-0), X_5 is $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$ or single bond.

Moreover, this invention also relates to the following:

(4) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein the compound represented by formula (I-0) is the formula (I-1)



[in the formula, R^{11} denotes phenyl which may be substituted with 1-3 R^4 or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4), and also

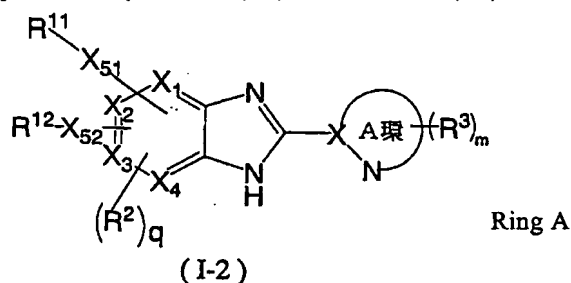
X_{51} denotes $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$, and the other symbols are the same as above].

Moreover, this invention also relates to the following:

- (5) a compound in accordance with aforesaid (4) or pharmacologically acceptable salts thereof, wherein in formula (I-1), both R^{11} are phenyl which may be substituted with 1-3 R^4 , or
- (6) a compound in accordance with aforesaid (4) or pharmacologically acceptable salts thereof, wherein in formula (I-1), both R^{11} are 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4), or
- (7) a compound in accordance with aforesaid (4) or pharmacologically acceptable salts thereof, wherein in formula (I-1), one of the R^{11} is phenyl which may be substituted with 1-3 R^4 and also the other R^{11} is 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4).

Furthermore, this invention also relates to the following:

- (8) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein the compound represented by formula (I-0) is the formula (I-2)



[in the formula, R^{11} denotes phenyl which may be substituted with 1-3 R^4 or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4),

R^{12} denotes 4 to 7-membered nitrogen-containing heteroring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said R^{12} may be substituted with 1-3 R^4 , and moreover, when the said hetero ring is an aliphatic hetero ring, it may contain 1 or 2 double bonds),

X_{51} is -O-, -S-, -S(O)- or -S(O)₂-,

X_{52} is -O-, -S-, -S(O)-, -S(O)₂- or single bond, and the other symbols are the same as above].

Moreover, this invention also relates to the following:

- (9) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2), R^{12} is 4 to 7-membered nitrogen-containing saturated aliphatic hetero

ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3 R^4) and also X_{52} is a single bond, or

R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4) and also X_{52} is -O-, -S-, -S(O)- or -S(O)₂-,

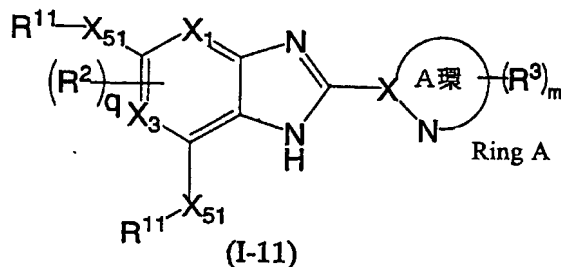
(10) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2), R^{12} is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3 R^4) and also X_{52} is a single bond, or

(11) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2), R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4) and also X_{52} is -O-, -S-, -S(O)- or -S(O)₂-,

(12) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2), R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4) and also X_{52} is -O-.

Moreover, this invention also relates to the following:

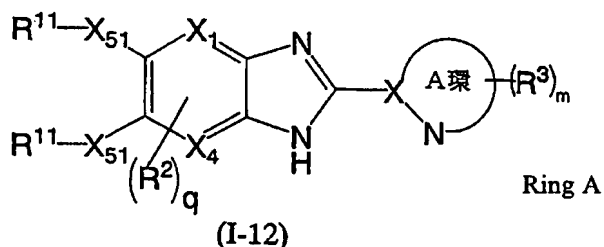
(13) a compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-11)



(each symbol is the same as above),

(14) a compound in accordance with aforesaid (13) or pharmacologically acceptable salts thereof, wherein in formula (I-12), both X_{51} are -O-,

(15)) a compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-12)

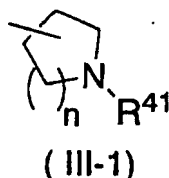


(each symbol is the same as above),

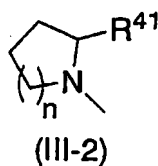
(16) a compound in accordance with aforesaid (15) or pharmacologically acceptable salts thereof, wherein in formula (I-12), both X_{51} are -O-.

Moreover, this invention also relates to the following:

(17) a compound in accordance with aforesaid (10) or pharmacologically acceptable salts thereof, wherein R^{12} in formula (I-2) is formula (III-1)



or formula (III-2)



[wherein, n denotes an integer of 1-3, and R^{41} denotes the group same as the aforesaid R^4].

Moreover, this invention also relates to the following:

(18) a compound in accordance with any one of aforesaid (1) to (17) or pharmacologically acceptable salts thereof, wherein the A ring is thiazolyl, imidazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, pyrazolyl or pyrimidinyl which may be substituted with 1-3 of aforesaid R^4 .

Moreover, this invention also relates to the following:

(19) a compound or pharmacologically acceptable salts thereof, wherein the compound

represented by formula (I-0) is

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole,
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole,
5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
,
5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
,
5-(2,6-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
,
5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-cyanopyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-

benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole,

5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2-fluoro-phenoxy)-2-(pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole,

4-(2-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,3-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

,
4-(2,5-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole
,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
1-(2-(6-(5-bromo-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide,
2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile,
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylamino-ethanone,
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
N-(5-(6-[1-acetyl-pyrrolidin-2-yl]-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide,
1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

N-(2-(2-[6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl]-pyrrolidin-1-yl)-2-oxo-ethyl)-acetamide,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • mono trifluoroacetate,
1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridine-2(1H)-one,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
(2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine,
6-(1-acetylpyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(1-acetyl-3-fluoropyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(6-(methoxymethylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol,
2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide,
5'-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one,
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,
6-(1-acetylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetyl-3-fluoropyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)

oxy)-2-pyridin-2-yl-1H-benzimidazole,
 3-(4-((6-(1-acetylpiperidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy)
 phenyl)-1,3-oxazolidin-2-one,
 6-(1-acetylpiperidin-2-yl)-2-pyrazin-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl)
 oxy)-1H-benzimidazole,
 6-(1-acetylpiperidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)
 oxy)-2-pyrazin-2-yl-1H-benzimidazole,
 1-(4-((6-(1-acetyl piperidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone,
 6-(1-acetylpiperidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl)
 phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
 6-(1-acetyl-5-methylpiperidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzi
 midazole,
 N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)
 piperidin-1-yl)-2-oxo ethanamine,
 6-(1-acetyl-5-methylpiperidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl)
 oxy)-2-pyrazin-2-yl-1H-benzimidazole,
 1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-piperidin-2-yl)-et
 hanone,
 1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-piperidin-
 2-yl)-ethanone,
 1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-piperidin-2-yl
)-ethanone, or
 1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrro
 lidin-2-yl)-ethanone.

Moreover, this invention also relates to the following:

(20) a medicinal composition comprising the following (1)-(3) to be used for therapy, prevention
 and/or delay of onset of type II diabetes mellitus;

- (1) a compound in accordance with any one of the said (1) to (19),
- (2) a compound of 1 or 2 or more, selected from the group comprising following (a)-(h),
 - (a) other glucokinase activator,
 - (b) bis-guanide,
 - (c) PPAR agonist,
 - (d) insulin,
 - (e) somatostatin,
 - (f) α -glucosidase inhibitor,
 - (g) insulin, and
 - (h) DPF-IV (dipeptidyl peptidase IV) inhibitor

- (3) a pharmacologically acceptable carrier,
(21) a glucokinase activator containing as effective ingredient a compound in accordance with any one of the said (1) to (19) or pharmacologically acceptable salts thereof,
(22) a therapeutic and/or preventive agent of diabetes mellitus containing as effective ingredient a compound in accordance with any one of the said (1) to (20) or pharmacologically acceptable salts thereof, or
(23) a therapeutic and/or preventive agent of obesity containing as effective ingredient a compound in accordance with any one of the said (1) to (20) or pharmacologically acceptable salts thereof.

Ideal form for Carrying Out the Invention

Below the meanings of the terms used in this specification are explained, and the compounds in accordance with this invention are described in further detail.

In this specification, as following group, the species listed below can be nominated unless specified in particular.

As "aryl", hydrocarbon aromatic ring of carbon number 6-14 is meant preferably, and for example phenyl, naphthyl, biphenyl, anthryl and the like are proposed, among these, phenyl, naphthyl or biphenyl are preferred, and phenyl is more preferred.

As "C₁₋₆ alkyl", C₁₋₆ alkyl containing straight chain or divergence is denoted, and for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, neopentyl, isopentyl, 1,1-dimethylpropyl, 1-methyl butyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methyl pentyl, 2-methyl pentyl, 3-methyl pentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethyl butyl, 1,3-dimethyl butyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethyl butyl, 2-ethyl butyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and the like may be proposed.

As "C₂₋₆ alkenyl", C₂₋₆ alkenyl having a straight or branched chain is denoted, and for example, allyl, 2-propenyl, 1-butenyl, 2-butenyl, 2-methyl-2-butenyl, 1-pentenyl and the like may be proposed.

As "C₃₋₇ cycloalkyl", for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like may be proposed.

As "halogen", fluorine, chlorine, bromine or iodine is denoted.

As " $-(CH_2)_{1-6}-OH$ ", hydroxymethylene, hydroxy ethylene and the like may be proposed.

As " $-O-C_{1-6}$ alkyl", for example, methoxy, ethoxy, propoxy or tert butoxy and the like may be proposed.

As " $-(CH_2)_{1-6}-OC_{1-6}$ alkyl", methoxymethyl, methoxyethyl, propyloxy methyl, isopropyl oxymethyl and the like may be proposed.

As, " $-C(O)_{1-6}$ alkyl", acetyl, ethyl carbonyl, isopropyl carbonyl, propyl carbonyl and the like may be proposed.

As " $-C(O)OC_{1-6}$ alkyl", for example, methoxycarbonyl, ethoxycarbonyl or tert butoxycarbonyl and the like may be proposed.

As " $-(CH_2)_{1-6}-NH_2$ ", aminomethyl, aminoethyl, aminopropyl and the like may be proposed.

As " $-NH-C_{1-6}$ alkyl", for example, methylamino, ethylamino, propylamino or 2-methyl butyl-amino and the like may be proposed.

As " $-N-di-(C_{1-6}$ alkyl)", it is meant a group in which the same or different aforesaid definition of " C_{1-6} alkyl" and N are linked, and for example dimethylamino, ethyl propylamino, 2-methyl butyl-1-methylamino and the like may be proposed. Moreover, the same or different C_{1-6} alkyl in the " $-N-di-(C_{1-6}$ alkyl)" may form a ring together with nitrogen atom, and for example piperidine, pyrrolidine and the like are nominated as embodiment of the said ring.

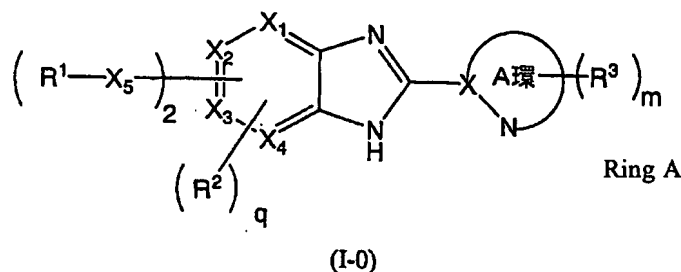
" $-CH_3-aF_a$ " means a group in which the 1-3 hydrogen atoms in methyl are substituted by fluorine atom, and for example, trifluoromethyl, difluoromethyl or fluoromethyl and the like may be proposed.

" $-OCH_3-aF_a$ " denotes a group in which oxygen atom is combined with " $-CH_3-aF_a$ " of the said definition, and for example trifluoromethoxy, difluoromethoxy or fluoromethoxy and the like may be proposed.

The a denotes an integer of 1-3.

In order to disclose further using examples of compounds in accordance with this invention, various notations used in formula (I-0), (I-1), (I-2), (I-11) or (I-12) will be explained with examples.

The compound represented by formula (I-0) in accordance with this invention will be explained.



X₅ denotes -O-, -S-, -S(O)-, -S(O)₂-, single bond or -O-C₁₋₆-alkyl.

R¹ denotes aryl or a 4-10 membered monocyclic or bicyclic nitrogen-containing heterorings containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring.

As "aryl" of the R¹, the same aryl as the aforesaid definition may be proposed, and phenyl, naphthyl or biphenyl are preferred, and phenyl is more preferred.

As "4-7 membered monocyclic or 9 or 10 membered condensed heteroring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring" of the R¹, it is meant a monocycle of 4- 7- membered ring as the ring or 9- or 10-memebred bicyclic ring of aliphatic hetero ring or aromatic hetero ring wherein 1 to 4 of the ring constituting atoms are heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and the other atoms of the hetero ring constituting ring are carbon atoms.

When nitrogen atom is contained in the said hetero ring, said nitrogen atom may form N-oxide.

When 2 or 3 heteroatoms are present in the said hetero ring, these may be the same or different.

When the said hetero ring is aliphatic hetero ring, moreover, the methylene in the said hetero ring may be replaced with nitrogen atom, sulfur atom or oxygen atom, furthermore, the said sulfur atom mat be oxidized to form sulphenyl or sulfonyl.

As said hetero ring, for example, azetidiny, thiazolidiny, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, azepanyl, 2,5-dioxo pyrrolidinyl, 2-benzoxolinonyl, 1,1-dioxo tetrahydrothienyl, 2,4-dioxo imidazolidinyl, 2-oxo-[1,3,4]-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodioxoly, [1,2,4]-oxadiazolinyl, 2-azabicyclo [2.2.1] heptyl, 4-thiazolidonyl,

morpholinino, 2-oxo tetrahydrofuranyl, tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, isoxazolyl, tetrahydropyranyl, piperidyl, 1-oxo-1,3-dihydroiso indolyl, piperaziny, thiomorpholino, 1,1-dioxo thiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperaziny, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiazolyl, thiadiazolyl, isothiazolyl, [1,2,4]-triazolyl, [1,2,3]-triazolyl, pyranyl, indolyl, pyrimidinyl, thiazolyl, pyraziny, pyridaziny, pyridyl, 4-pyridonyl, quinolyl or iso quinoliny may be proposed.

Among these, as 4-7 membered monocyclic hetero ring, for example, azetidiny, isoxazolyl, pyrrolidinyl, 2-pyrrolidonyl, 2,5-dioxo pyrrolidonyl, morpholino, tetrahydrofuranyl, azepanyl, piperidyl, piperaziny, thiomorpholino, tetrahydropyranyl, imidazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyrazolyl, indolyl, thiazolyl, thiadiazolyl, pyraziny, pyridaziny, pyridyl and the like may be proposed.

Among these, as 4-7 membered monocyclic aliphatic hetero ring, for example, azetidiny, pyrrolidinyl, piperidyl, piperidinyl, azepanyl, piperaziny, morpholino, thiomorpholino, homopiperaziny, imidazolidiny, pyrazolidiny and the like may be proposed.

Among these, as 5 or 6 membered monocyclic heteroaromatic ring, for example, pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyraziny, pyrimidinyl, pyridaziny and the like may be proposed.

Among these, 9 or 10 membered condensed hetero ring, for example benzofuranyl, benzimidazolyl, benzothiophenyl, benzothiazolyl, benzo isothiazolyl, benzoxazolyl, benzo isoxazolyl, pyrido imidazolyl, quinolyl, isoquinolyl, quinoxaliny, quinazolinyl, phthalidinyl, cinnolinyl, indolyl, indazolyl, puriny, indoliziny, isoindolyl, pteridinyl, naphthyridiny and the like are proposed.

As the said hetero ring, 4-7 membered monocyclic aliphatic hetero ring in which the at least one of the said hetero ring constituting atom is nitrogen atom or 5 or 6 membered heteroaromatic ring is preferred.

R¹ may be substituted with 1-3 R⁴.

Wherein, R⁴ each independently denotes

- C₁₋₆ alkyl (the said alkyl may be substituted with the same or different 1 to 3 hydroxy, halogen,
- OC(O)-C₁₋₆ alkyl (the said alkyl may be substituted with 1 to 3 halogen), or -OC₁₋₆ alkyl)
- C₃₋₈ cycloalkyl,
- C₂₋₆ alkenyl,

$-C(O)-N(R^{51})R^{52}$,
 $-S(O)_2-N(R^{51})R^{52}$,
 $-O-C_{1-6}$ alkyl (the said C_{1-6} alkyl may be substituted with halogen or $N(R^{51})R^{52}$),
 $-S(O)_{0-2}-C_{1-6}$ alkyl,
 $-C(O)-C_{1-6}$ alkyl (the said C_{1-6} alkyl may be substituted with halogen, amino, CN, hydroxy, $-O-C_{1-6}$ alkyl, $-CH_3-Fa$, $-OC(O)-C_{1-6}$ alkyl, $-N(C_{1-6} \text{ alkyl})C(O)O-C_{1-6}$ alkyl, $-NH-C(O)O-C_{1-6}$ alkyl, phenyl, $-N(R^{51})R^{52}-NH-C(O)-C_{1-6}$ alkyl, $-N(C_{1-6} \text{ alkyl})-C(O)-C_{1-6}$ alkyl or $-NH-S(O)_{0-2}-C_{1-6}$ alkyl),
 $-C(S)-C_{3-7}$ cycloalkyl,
 $-C(S)-C_{1-6}$ alkyl,
 $-C(O)-O-C_{1-6}$ alkyl,
 $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$,
 $-N(R^{53})-C(O)-O-R^{54}$,
 $-C(O)-\text{aryl}$ (the said aryl may be substituted with halogen),
 $-C(O)-\text{heteroaromatic ring}$,
 $-C(O)-\text{aliphatic hetero ring}$,
hetero ring (the said hetero ring may be substituted with $-C_{1-6}$ alkyl (the said $-C_{1-6}$ alkyl may be substituted with halogen or $-O-C_{1-6}$ alkyl),
phenyl (the said phenyl may be substituted with halogen, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl),
halogen, CN, formyl, COOH, amino, oxo, hydroxy, hydroxy amidino or nitro.

As "halogen" of R^4 denotes the same group as in the aforesaid definition.

As " $-C_{1-6}$ alkyl" of R^4 denotes an alkyl of carbon number 1-6 having straight chain or branching, and for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, neopentyl, isopentyl, 1,1-dimethylpropyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methyl pentyl, 2-methyl pentyl, 3-methyl pentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethyl butyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethyl butyl, 1-ethyl butyl, 2-ethyl butyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and the like may be proposed.

The said " $-C_{1-6}$ alkyl" may be substituted with 1-3 hydroxy, halogen, $-OC(O)-C_{1-6}$ alkyl (the said alkyl may be substituted with 1-3 halogen) or $-O-C_{1-6}$ alkyl.

When the said " $-C_{1-6}$ alkyl" contains 2 or 3 of the aforesaid substituent, these may be the same or different.

As halogen of said substituent, the same group as in the aforesaid definition may be proposed.

As $-OC(O)-C_{1-6}$ alkyl of said substituent, for example, methylcarbonyloxy, ethylcarbonyloxy, isopropylcarbonyloxy and the like may be proposed.

The $-OC(O)-C_{1-6}$ alkyl of said substituent may be substituted with 1-3 halogen atoms of the aforesaid definition.

As $-O-C_{1-6}$ alkyl of said substituent, for example, methoxy, ethoxy, propoxy, isopropoxy and the like may be proposed.

The " $-S(O)_{0-2}-C_{1-6}$ alkyl" denoted by R^4 means a group in which the C_{1-6} alkyl of the said definition is combined with $-S(O)_{0-2}-$, and for example $-S$ -ethyl, $-S$ -methyl, $-S$ -isopropyl, $-S$ -propyl, $-S(O)_2$ -methyl, $-S(O)_2$ -ethyl and the like may be proposed.

The C_{1-6} alkyl in said " $-S(O)_{0-2}-C_{1-6}$ alkyl" may be substituted with hydroxy.

As " $-C_{3-8}$ cycloalkyl" of R^4 , the same groups as in the aforesaid definition may be proposed.

As " $-C_{2-6}$ alkenyl" of R^4 , the same groups as in the aforesaid definition may be proposed.

The " $C(O)N(R^{51})R^{52}$ " of R^4 , means a substituted or unsubstituted carbamoyl group, or a group in which carbonyl and 4-7 membered aliphatic hetero ring formed by linking N, R^{51} and R^{52} together.

Among the " $C(O)N(R^{51})R^{52}$ " of R^4 , as the substituted carbamoyl which is substituted or unsubstituted, for example, carbamoyl, methyl carbamoyl, ethyl carbamoyl, isopropyl carbamoyl, propyl carbamoyl, ethyl methyl carbamoyl, dimethyl carbamoyl, isopropyl methyl carbamoyl, diisopropyl carbamoyl, diethyl carbamoyl and the like may be proposed.

Among the " $C(O)N(R^{51})R^{52}$ " of R^4 , as the 4-7 membered aliphatic group, for example, azetidiny, pyrrolidinyl, piperidino, piperazinyl, morpholino and the like may be proposed. Accordingly, as $C(O)N(R^{51})R^{52}$, azetidine-1-carbonyl, pyrrolidine-1-carbonyl, piperidine-1-carbonyl, piperazine-1-carbonyl, morpholine-1-carbonyl and the like may be proposed.

As " $-C(O)-O-C_{1-6}$ alkyl" of R^4 , the same group as in " $-C(O)-O-C_{1-6}$ alkyl" of the said definition may be proposed.

As " $-O-C_{1-6}$ alkyl" of R^4 , the same group as in " $-O-C_{1-6}$ alkyl" of the said definition may be

proposed.

The said -O-C₁₋₆ alkyl may be substituted with halogen or N(R⁵¹)R⁵².

As "-C(O)-C₁₋₆ alkyl" of R⁴, the same group as in "-C(O)-C₁₋₆ alkyl" of the said definition may be proposed.

The said "-C(O)-C₁₋₆ alkyl" may be substituted with halogen, amino, -CH_{3-a}F_a, CN, hydroxy, -O-C₁₋₆ alkyl, -O-C(O)-C₁₋₆ alkyl, -N-(C₁₋₆ alkyl)-C(O)O-C₁₋₆ alkyl, -NH-C(O)O-C₁₋₆ alkyl, phenyl, -N(R⁵¹)R⁵²-NH-C(O)-C₁₋₆ alkyl, -N-(C₁₋₆ alkyl)-C(O)-C₁₋₆ alkyl or -NH-S(O)₀₋₂-C₁₋₆ alkyl.

As "halogen" of the said substituent, the same group as in halogen of the said definition may be proposed.

As "-CH_{3-a}F_a" of the said substituent, the same group as in "-CH_{3-a}F_a" of the said definition may be proposed.

As "-O-C₁₋₆ alkyl" of the said substituent, the same group as in "-O-C₁₋₆ alkyl" of the said definition may be proposed.

As "-O-C(O)-C₁₋₆ alkyl" of the said substituent, the same group as in the said "-O-C(O)-C₁₋₆ alkyl" may be proposed.

The "-N-(C₁₋₆ alkyl)-C(O)O-C₁₋₆ alkyl" of the said substituent means a group in which the said -C(O)O-C₁₋₆ alkyl is combined with -N-(C₁₋₆ alkyl)-, and for example -N(Me)-C(O)O-tert-butyl and the like may be proposed.

The "-NH-C(O)O-C₁₋₆ alkyl" of the said substituent means a group in which the said -C(O)O-C₁₋₆ alkyl is combined with -NH-, and for example, -NH-C(O)O-methyl, -NH-C(O)O-ethyl, -NH-C(O)O-isopropyl-NH-C(O)-propyl and the like may be proposed.

As "-N(R⁵¹)R⁵²" of the said substituent, the same group as in the said "-N(R⁵¹)R⁵²" may be proposed.

The "-NH-C(O)-C₁₋₆ alkyl" of said substituent means a group in which -NH-C(O)- and the aforesaid -C₁₋₆ alkyl are combined, and for example, -NH-C(O)-methyl, -NH-C(O)-ethyl, -NH-C(O)-isopropyl, -NH-C(O)-propyl and the like may be proposed.

The "-N-(C₁₋₆ alkyl)-C(O)-C₁₋₆ alkyl" of said substituent means a group in which C₁₋₆ alkyl of the said definition is combined with -N-(C₁₋₆ alkyl-C(O)-, and for example, -N(methyl)-C(O)-methyl, -N(methyl)-C(O)-ethyl, -N(ethyl)-C(O)-isopropyl, -N(methyl)-C(O)-isopropyl, -N(isopropyl)-C(O)-methyl and the like may be proposed.

The NH-S(O)₀₋₂-C₁₋₆ alkyl of said substituent denotes a group in which the said -S(O)₀₋₂-C₁₋₆ alkyl is combined with -NH-, and for example -NH-S(O)₂-methyl, -NH-S(O)₂-ethyl, -NH-S(O)₂-isopropyl and the like may be proposed.

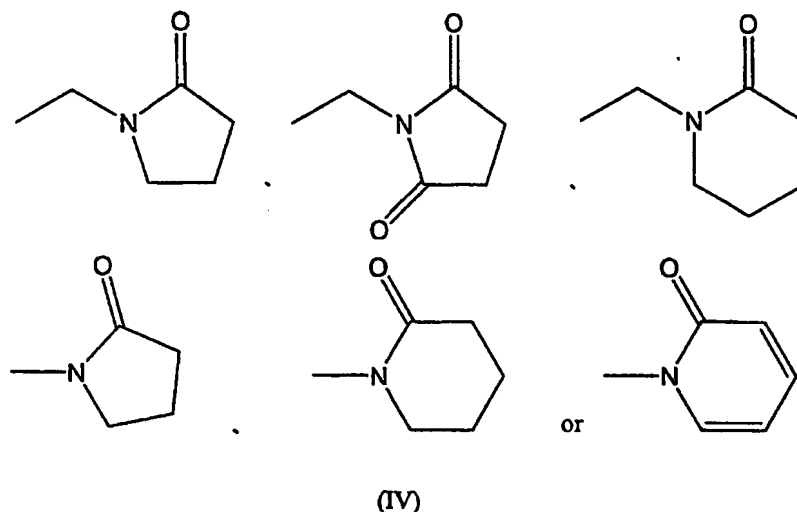
As "-C(O)-C₁₋₆ alkyl" that may contain on the said substituent on 1-6C alkyl, for example, fluoromethyl carbonyl, 2,2,2-trifluoroethyl carbonyl, cyanomethyl carbonyl, hydroxymethyl carbonyl, 2-hydroxyethyl carbonyl, methoxymethyl carbonyl, aminomethyl carbonyl, N-methylamino carbonyl, 2-phenylethyl carbonyl and the like may be proposed.

The "-C(S)-C₁₋₆ alkyl" of R⁴ denotes a group in which "-C₁₋₆ alkyl" of the said definition is combined with -C(S)-, and for example, -C(S)-methyl, -C(S)-ethyl, -C(S)-isopropyl, -C(S)-propyl and the like may be proposed.

In "-(CH₂)₀₋₄-N(R⁵³)-C(O)-R⁵⁴" of R⁴, ring R⁵³ denotes a hydrogen atom or C₁₋₆ alkyl, R⁵⁴ denotes C₁₋₆ alkyl or in the -N(R⁵³)-C(O)-R⁵⁴ of the "-(CH₂)₀₋₄-N(R⁵³)-C(O)-R⁵⁴", -N-C(O)- and alkyl of R⁵³ and R⁵⁴ are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring (the said hetero ring may be substituted with oxo, and moreover 1 or 2 double bonds may be contained in the ring).

As "-(CH₂)₀₋₄-N(R⁵³)-C(O)-R⁵⁴" when R⁵³ is hydrogen atom or -C₁₋₆ alkyl and R⁵⁴ is -C₁₋₆ alkyl, for example, -CH₂-NH-C(O)-methyl, -CH₂-NH-C(O)-ethyl, -CH₂-NH-C(O)-isopropyl, -CH₂-NH-C(O)-propyl, -CH₂-N(methyl)-C(O)-methyl, -CH₂-N(ethyl)-C(O)-methyl, -NH-C(O)-methyl, -NH-C(O)-ethyl, -NH-C(O)-isopropyl, -NH-C(O)-propyl, -N(methyl)-C(O)-methyl, -N(ethyl)-C(O)-methyl and the like may be proposed.

As "-(CH₂)₀₋₄-N(R⁵³)-C(O)-R⁵⁴" when -N-C(O)- and alkyl of R⁵³ and R⁵⁴ are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring (the said hetero ring may be substituted with oxo, and moreover 1 or 2 double bonds may be contained in the ring), for example, groups represented by formula

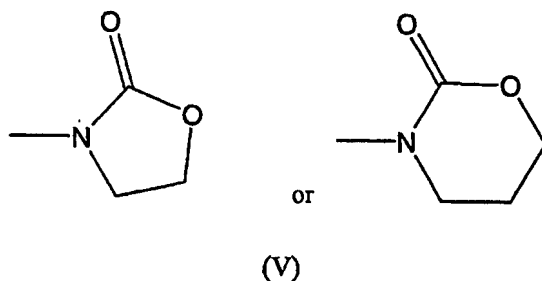


or the like may be proposed.

In " $-N(R^{55})-C(O)-O-R^{56}$ " of R^4 , R^{55} denotes hydrogen atom or $-C_{1-6}$ alkyl and R^{56} denotes $-C_{1-6}$ alkyl, or in " $-N(R^{55})-C(O)-O-R^{56}$ " of the " $-N(R^{55})-C(O)-CO-R^{56}$ ", $-N-C(O)-O-$ and R^{55} and R^{56} are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring.

As " $-N(R^{55})-C(O)-O-R^{56}$ " when R^{55} is hydrogen atom or $-C_{1-6}$ alkyl and R^{56} is $-C_{1-6}$ alkyl, for example, $-NH-C(O)-O$ -methyl, $-NH-C(O)-O$ -ethyl, $-NH-C(O)-CO$ -isopropyl, $-NH-C(O)-CO$ -propyl, $-N$ (methyl)- $C(O)-O$ -methyl, $-N$ (ethyl)- $C(O)-O$ -methyl and the like may be proposed.

As " $-N(R^{55})-C(O)-O-R^{56}$ " when $-N-C(O)-O-$ and R^{55} and R^{56} are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring, for example, groups represented by formula (V)



or the like may be proposed.

The " $-C(O)$ -aryl" of R^4 means a group in which the aryl of the said definition denotes is combined with carbonyl, and for example benzoyl, naphthyl carbonyl and the like may be proposed.

Moreover, the aryl in said "-C(O)-aryl" may be substituted with 1-3 halogen atoms of the said definition.

When 2 or 3 of the said halogens of said substituents are present, these may be the same or different.

The "-C(O)-heteroaromatic ring" of R^4 means a group in which carbonyl is combined with 5 or 6 membered monocyclic heteroaromatic ring or 9 or 10 membered bicyclic heteroaromatic ring of the said definition, and for example, -C(O)-pyrrolyl, -C(O)-furyl, -C(O)-thienyl, -C(O)-C(O)-pyrazolyl, -C(O)-isoxazolyl, -C(O)-iso thiazolyl, -C(O)-imidazolyl, -C(O)-oxazolyl, -C(O)-thiazolyl, -C(O)-triazolyl, -C(O)-oxadiazolyl, -C(O)-thiadiazolyl, -C(O)-tetrazolyl, -C(O)-pyridyl, -C(O)-pyrazinyl, -C(O)-pyrimidinyl, -C(O)-pyridazinyl and the like may be proposed.

The "-C(O)-heteroaromatic ring" of R^4 means a group in which carbonyl is combined with 4-7 membered monocyclic aliphatic hetero ring of the said definition, and for example, -C(O)-azetidiny, -C(O)-pyrrolidinyl, -C(O)-piperidine, -C(O)-piperidinyl, -C(O)-azepanyl, -C(O)-piperazinyl, -C(O)-morpholino, -C(O)-thiomorpholino, -C(O)-homopiperazinyl, -C(O)-imidazolidinyl, -C(O)-pyrazolidinyl and the like may be proposed.

As "hetero ring" of R^4 , the same group as "hetero ring" of R^1 may be proposed.

Moreover, the said hetero ring may be substituted with 1-3 of -C₁₋₆-alkyl, halogen or -O-C₁₋₆-alkyl.

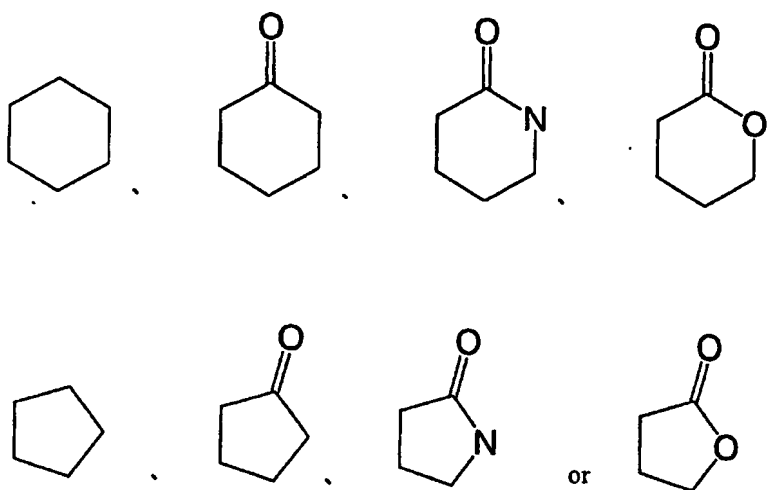
When 2 or 3 of the said substituent are present, these may be the same or different.

As the -C₁₋₆-alkyl, halogen and -O-C₁₋₆-alkyl of the said substituent, the groups same as in the groups defined as above may be proposed.

As "the halogen" of R^4 , the same groups as in "halogen" of the said definition may be proposed.

The "phenyl" of R^4 may be substituted with halogen, -C₁₋₆-alkyl or -O-C₁₋₆-alkyl.

When R^1 has 2 or 3 R^4 as substituents, the two of the same or different R^4 may be linked together, to form a 4-6 membered ring, and for example, groups represented by formula (VI)



(VI)

may be proposed.

-X5-denotes -O-, -S-, -S(O)-, -S(O)₂-, single bond or -O-C₁₋₆-alkyl.

As -X5-, -O-, -S-, -S(O)-, -S(O)₂- or single bond is preferred.

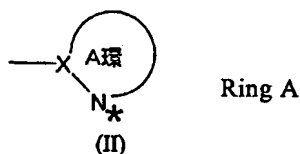
As R¹-X₅- (the said R¹ may be substituted with 1-3 of the aforesaid R₄), for example, phenyl sulphonyl, phenoxy, benzyloxy, phenethyl oxy, 2-cyano phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 2-cyano-6-fluoro phenoxy, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-fluoro-6-carbamoyl phenoxy, 2-methylcarbamoyl phenoxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 2-methoxy-phenoxy, 3-methoxyphenoxy, 4-methoxyphenoxy, 4-methoxymethyl phenoxy, 2-isopropyl phenoxy, 3-isopropyl phenoxy, 4-isopropyl phenoxy, 2-methylphenoxy, 3-methylphenoxy, 4-methylphenoxy, 2-ethyl phenoxy, 3-ethyl phenoxy, 4-ethyl phenoxy, 2-acetyl phenoxy, 3-acetyl phenoxy, 4-acetyl phenoxy, 2-methanesulphonyl-phenoxy, 3-methanesulphonyl phenoxy, 3-chloro-4-methanesulphonyl phenoxy, 4-methanesulphonyl phenoxy, 2-ethanesulphonyl phenoxy, 3-ethanesulphonyl phenoxy, 4-ethanesulphonyl phenoxy, 2-methoxycarbonyl phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-ethoxycarbonyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-hydroxyphenoxy, 3-hydroxyphenoxy, 4-hydroxyphenoxy, 2-hydroxymethyl phenoxy, 3-hydroxymethyl phenoxy, 4-hydroxymethyl phenoxy, 2-hydroxyethyl phenoxy, 3-hydroxyethyl phenoxy, 4-hydroxyethyl phenoxy, 2-formyl phenoxy, 3-formyl phenoxy, 4-formyl phenoxy, 2-(1-hydroxyethyl) phenoxy, 3-(1-hydroxyethyl) phenoxy, 4-(1-hydroxyethyl) phenoxy, 2,3-difluoro phenoxy, 2,5-difluoro phenoxy, 2,4-difluoro phenoxy,

2,6-difluoro phenoxy, 2-fluoro phenoxy, 3-fluoro phenoxy, 4-fluoro phenoxy,
 2-di-fluoromethoxyphenoxy, 3-difluoromethoxyphenoxy, 4-difluoromethoxyphenoxy,
 2-trifluoromethoxyphenoxy, 3-trifluoromethoxyphenoxy, 4-trifluoromethoxyphenoxy,
 2-(1H-tetrazol-5-yl) phenoxy, 3-(1H-tetrazol-5-yl) phenoxy, 4-(1H-tetrazol-5-yl) phenoxy,
 4-(2-methyl-2H-tetrazol-5-yl) phenoxy, 2-(oxadiazol-3-yl) phenoxy, 3-(oxadiazol-3-yl) phenoxy,
 4-(oxadiazol-3-yl) phenoxy, 2-(5-methyl oxadiazol-3-yl) phenoxy, 3-(5-methyl oxadiazol-3-yl)
 phenoxy, 4-(5-methyl oxadiazol-3-yl) phenoxy, 2-methoxyphenyl sulphanyl, 3-methoxyphenyl
 sulphanyl, 4-methoxyphenyl sulphanyl, 2-methoxyphenylmethyl sulphanyl,
 3-methoxyphenylmethyl sulphanyl, 4-methoxyphenylmethyl sulphanyl
 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4]
 oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-(N-hydroxy
 amidino) phenoxy, 3-(N-hydroxy amidino) phenoxy, 4-(N-hydroxy amidino) phenoxy,
 2'-fluorobipheny-4-yloxy, pyridin-2-yl sulphanyl, pyridin-3-yl sulphanyl, pyridin-4-yl sulphanyl,
 pyridin-4-yl sulfonyl aminopyridin-2-yloxy, pyridin-2-yloxy, pyridin-3-yloxy, pyridine-4-yloxy,
 2-methoxypyridin-3-yloxy, 2-methoxypyridine-4-yloxy, 6-methoxypyridin-3-yloxy,
 6-methoxypyridin-2-yloxy, 3-methoxypyridin-2-yloxy, 4-methoxypyridin-2-yloxy,
 5-methoxypyridin-2-yloxy, 6-methoxymethyl pyridin-3-yloxy,
 2-difluoromethoxypyridin-3-yloxy, 4-difluoromethoxypyridin-3-yloxy, 6-methylpyridin-2-yl
 sulphanyl, 5-methylpyridin-2-yl sulphanyl, 4-methylpyridin-2-yl sulphanyl, 3-methylpyridin-2-yl
 sulphanyl, 4-cyano-pyridin-3-yloxy, 6-cyano-pyridin-3-yloxy,
 4-dimethylcarbamoyl-pyridin-3-yloxy, 6-methanesulphonyl-pyridin-3-yloxy,
 6-ethanesulphonyl-pyridin-3-yloxy, 4-methanesulphonyl-pyridin-3-yloxy,
 2-cyano-pyridin-3-yloxy, 2-dimethylcarbamoyl-pyridin-3-yloxy,
 2-methanesulphonyl-pyridin-3-yloxy, 2-methylpyridin-3-yl sulphanyl, 2-chloropyridin-3-yloxy,
 6-acetyl-amino-pyridin-3-yloxy, 2-oxo-2H-[1,3'] bipyridine-6'-yloxy, 4-methylpyridin-3-yl
 sulphanyl, 5-methylpyridin-3-yl sulphanyl, 6-methylpyridin-3-yl sulphanyl, 2-methylpyridin-4-yl
 sulphanyl, 3-methylpyridin-4-yl sulphanyl, 4-methylpyridin-3-yl sulfonyl, 5-methylpyridin-3-yl
 sulfonyl, 6-methylpyridin-3-yl sulfonyl, 2-methylpyridin-3-yl sulfonyl, 3-methylpyridin-2-yl
 sulfonyl, 4-methylpyridin-2-yl sulfonyl, 5-methylpyridin-2-yl sulfonyl, 6-methylpyridin-2-yl
 sulfonyl, 2-oxo-1,2-dihydropyridin-3-yloxy, 1-methyl-2-oxo-1,2-dihydropyridin-3-yloxy,
 1-ethyl-2-oxo-1,2-dihydropyridin-3-yloxy, 5-bromopyridin-2-yloxy, 6-(5-methyl-[1,2,4]
 oxadiazol-3-yl-pyridine)-3-yloxy, 6-([1,2,4] oxadiazol-3-yl-pyridine)-3-yloxy, 1H-imidazol-2-yl
 sulphanyl, 1-methyl-1H-imidazol-2-yl sulphanyl, 4H-[1,2,4] triazol-3-yl sulphanyl,
 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl, 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yloxy,
 5-(2-oxo-oxadiazolidin-3-yl) pyridin-2-yloxy, 6-pyrazin-2-yl-pyridin-3-yloxy, 1-acetyl
 pyrrolidin-2-yl, 2-acetyl pyrrolidin-1-yl, 1-acetyl-3-fluoro-pyrrolidin-2-yl,
 1-acetyl-5-methyl-pyrrolidin-2-yl, 1-acetyl piperidin-2-yl, 1-ethyl carbonyl-pyrrolidin-2-yl,
 2-ethyl carbonyl pyrrolidin-1-yl, 1-ethyl carbonyl-piperidin-2-yl, 1-n-propyl

carbonyl-pyrrolidin-2-yl, 2-n-propyl carbonyl-pyrrolidin-2-yl, 1-n-propyl carbonyl-piperidin-2-yl,
 1-isopropyl-pyrrolidin-2-yl, 2-isopropyl-pyrrolidin-1-yl, 1-isopropyl-piperidin-2-yl,
 1-hydroxyethyl carbonyl-pyrrolidin-2-yl, 2-hydroxyethyl carbonyl-pyrrolidin-1-yl,
 1-hydroxyethyl carbonyl-piperidin-2-yl, 1-hydroxymethyl carbonyl-pyrrolidin-2-yl,
 2-hydroxymethyl carbonyl-pyrrolidin-1-yl, 1-hydroxymethyl carbonyl-piperidin-2-yl,
 1-methoxymethyl carbonyl-pyrrolidin-2-yl, 2-methoxymethyl carbonyl-pyrrolidin-1-yl,
 1-methoxymethyl carbonyl-piperidin-2-yl, 1-ethoxymethyl carbonyl-pyrrolidin-2-yl,
 2-ethoxymethyl carbonyl-pyrrolidin-1-yl, 1-ethoxymethyl carbonyl-piperidin-2-yl,
 1-methylpyrrolidin-2-yl, 2-methylpyrrolidin-1-yl, 1-methylpiperidin-2-yl, 1-ethylpyrrolidin-2-yl,
 2-ethylpyrrolidin-1-yl, 1-ethylpiperidin-2-yl, 1-phenyl carbonyl-pyrrolidin-2-yl, 2-phenyl
 carbonyl-pyrrolidin-1-yl, 1-phenyl carbonyl-piperidin-2-yl, 1-phenethyl carbonyl-pyrrolidin-2-yl,
 2-phenethyl carbonyl-pyrrolidin-1-yl, 1-phenethyl carbonyl-piperidin-2-yl, 1-benzyl
 carbonyl-pyrrolidin-2-yl, 2-benzyl carbonyl-pyrrolidin-1-yl, 1-benzyl carbonyl-piperidin-2-yl,
 1-dimethylaminomethyl carbonyl-pyrrolidin-2-yl, 2-dimethylaminomethyl
 carbonyl-pyrrolidin-1-yl, 1-dimethylaminomethyl carbonyl-piperidin-2-yl, 1-methylaminomethyl
 carbonyl-pyrrolidin-2-yl, 2-methylaminomethyl carbonyl-pyrrolidin-1-yl, 1-methylaminomethyl
 carbonyl-piperidin-2-yl, 1-cyclohexyl carbonyl-pyrrolidin-2-yl, 2-cyclohexyl
 carbonyl-pyrrolidin-1-yl, 1-cyclohexyl carbonyl-piperidin-2-yl, 1-cyclopentyl
 carbonyl-pyrrolidin-2-yl, 2-cyclopentyl carbonyl-pyrrolidin-1-yl, 1-cyclopentyl
 carbonyl-piperidin-2-yl, 1-(1-methyl-3-oxobutyl carbonyl)-pyrrolidin-2-yl,
 2-(1-methyl-3-oxobutyl carbonyl)-pyrrolidin-1-yl, 1-(1-methyl-3-oxo butyl
 carbonyl)-piperidin-2-yl, 1-methanesulphonyl-pyrrolidin-2-yl,
 2-methanesulphonyl-pyrrolidin-1-yl, 1-methanesulphonyl-piperidin-2-yl,
 1-ethanesulphonyl-pyrrolidin-2-yl, 2-ethanesulphonyl-pyrrolidin-1-yl,
 1-ethanesulphonyl-piperidin-2-yl, 1-isopropyl sulfonyl-pyrrolidin-2-yl, 2-isopropyl
 sulfonyl-pyrrolidin-1-yl, 1-isopropyl sulfonyl-piperidin-2-yl, 1-carbamoyl-pyrrolidin-2-yl,
 2-carbamoyl-pyrrolidin-1-yl, 1-carbamoyl-piperidin-2-yl, 1-carbamoylmethyl-pyrrolidin-2-yl,
 2-carbamoylmethyl-pyrrolidin-1-yl, 1-carbamoylmethyl-piperidin-2-yl,
 1-carbamoylethyl-pyrrolidin-2-yl, 2-carbamoylethyl-pyrrolidin-1-yl,
 1-carbamoylethyl-piperidin-2-yl, 1-(pyrrolidine-2-ylcarbonyl) pyrrolidin-2-yl,
 2-(pyrrolidine-2-ylcarbonyl) pyrrolidin-1-yl, 1-(pyrrolidine-2-ylcarbonyl)-piperidin-2-yl,
 1-(pyrimidinyl-2-yl) pyrrolidin-2-yl, 2-(pyrimidinyl-2-yl) pyrrolidin-1-yl, 1-(pyrimidinyl-2-yl)
 piperidin-2-yl, 1-(pyrazinyl-2-yl) pyrrolidin-2-yl, 2-(pyrazinyl-2-yl) pyrrolidin-1-yl,
 1-(pyrazinyl-2-yl) piperidin-2-yl, 1-(pyridyl-2-yl) pyrrolidin-2-yl, 2-(pyridyl-2-yl) pyrrolidin-1-yl,
 1-(pyridyl-2-yl) piperidin-2-yl, 1-(pyridyl-3-yl) pyrrolidin-2-yl, 2-(pyridyl-3-yl) pyrrolidin-1-yl,
 1-(pyridyl-3-yl) piperidin-2-yl, 1-trifluoromethyl carbonyl-pyrrolidin-2-yl, 2-trifluoromethyl
 carbonyl-pyrrolidin-1-yl, 1-trifluoromethyl carbonyl-piperidin-2-yl, 1-(2-hydroxyacetyl)
 pyrrolidin-2-yl, 2-(2-hydroxyacetyl) pyrrolidin-1-yl, 1-(2-hydroxyacetyl) piperidin-2-yl,

1-(2-methylamino acetyl) pyrrolidin-2-yl, 2-(2-methylamino acetyl) pyrrolidin-1-yl, 1-(2-methylamino acetyl) piperidin-2-yl, 1-(2-dimethylamino acetyl) pyrrolidin-2-yl, 2-(2-dimethylamino acetyl) pyrrolidin-1-yl, 1-(2-dimethylamino acetyl) piperidin-2-yl, 1-n-propylamino acetyl-pyrrolidin-2-yl, 2-n-propylamino acetyl-pyrrolidin-1-yl, 1-n-propylamino acetyl-piperidin-2-yl, 1-isopropyl-amino acetyl-pyrrolidin-2-yl, 2-isopropyl-amino acetyl-pyrrolidin-1-yl, 1-isopropyl-amino acetyl-piperidin-2-yl and the like may be proposed.

The A ring denotes 5-6 membered nitrogen-containing heteroaromatic ring which may contain 1-3 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring represented by formula (II) (nitrogen atom represented by N* in the formula II is excluded)



or the group condensed the said 5-6 membered heteroaromatic ring and phenyl or pyridyl.

X denotes a carbon atom or nitrogen atom.

As the A ring when it is 5-6 membered nitrogen containing heteroaromatic ring in a further embodiment, for example, thiazolyl, imidazolyl, isothiazolyl, thiadiazolyl, triazolyl, oxazolyl, oxadiazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, pyrazolyl, pyrimidinyl and the like are proposed, and among these, thiazolyl, thidiazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, triazolyl or pyrazolyl are preferred, and pyridyl, pyrazinyl, thiazolyl, thiadiazolyl, isoxazolyl or pyrazolyl are more preferred.

As a further embodiment as the A ring when it is bicyclic in which 5-6 membered nitrogen-containing aromatic ring and phenyl or pyridyl are condensed, for example, indolyl, benzimidazolyl, benzoxazolyl, pyrido thiazolyl or benzothiazolyl are proposed.

As A ring, 5-6 membered nitrogen-containing aromatic heterocycle is preferred.

Moreover, the said A ring may contain 1 or 2 substituents represented by R³ described above in said ring, and when 2 substituents are present on A ring, these may be the same or different.

As R³, for example, methyl, ethoxy, hydroxymethyl, methoxycarbonyl, methoxymethyl, aminomethyl, cyano, acetyl, fluorine, chlorine, bromine or difluoromethyl and the like may be proposed.

Thus, as the A ring (the said A ring may be 1-3 substituted with R³), in further embodiment, for example 3H-imidazol-4-yl, 1H-imidazol-2-yl, [1,2,4] triazol-3-yl, [1,2,3] triazol-4-yl, pyrazol-3-yl, pyrazol-1-yl, pyridin-2-yl, pyrazin-2-yl, oxazol-2-yl, oxazol-4-yl, [1,2,4] thiadiazol-5-yl, [1,2,4] thiadiazol-3-yl, thiazol-2-yl, thiazol-4-yl, [1,2,5] thiadiazol-3-yl, pyrrole-2-yl, iso thiazol-3-yl, isoxazol-3-yl, 4-methyl-thiazol-2-yl, 4-hydroxymethyl-thiazol-2-yl, 4-methoxycarbonyl-thiazol-2-yl, 4-methoxymethyl-thiazol-2-yl, 4-aminomethyl-thiazol-2-yl, 4-cyano-thiazol-2-yl, 4-cyano-thiazol-2-yl, 4-fluoro-thiazol-2-yl, imidazol-2-yl, 4-methyl-imidazol-2-yl, 4-methoxycarbonyl-imidazol-2-yl, isothiazol-3-yl, 4-hydroxymethyl-isothiazol-3-yl, [1,3,4] thiadiazol-2-yl, 5-acetyl-[1,3,4] thiadiazol-2-yl, [1,2,4] triazol-2-yl, 5-hydroxymethyl-[1,2,4] triazol-3-yl, 4-methyl-pyridin-2-yl, 4-methoxymethyl-imidazol-2-yl, 4-acetyl-imidazol-2-yl, 5-hydroxymethyl-imidazol-2-yl, 5-methyl-[1,3,4] thiadiazol-2-yl, 5-fluoro-[1,3,4] thiadiazol-2-yl, 5-methyl-[1,2,4] triazol-2-yl, 5-acetyl-[1,2,4] triazol-3-yl, 4-methoxymethyl-isoxazol-2-yl, 5-methyl-isoxazol-3-yl, 5-hydroxymethyl-isoxazol-3-yl, 1-oxy-pyrazin-2-yl, 1-oxy-pyridin-2-yl, 5-methoxymethyl-isoxazol-3-yl, 5-methyl carbonyl-isoxazol-3-yl, 5-chloro-isoxazol-3-yl, 5-aminomethyl-isoxazol-3-yl, 4 methyl-1H-pyrazol-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridazin-3-yl, 6-methyl-pyridazin-3-yl, 2-methyl-thiazol-4-yl, thiazolo [5,4-b] pyridin-2-yl, 3-methyl-[1,2,4] thiadiazolyl-5-yl, 1-methyl-1H-pyrazol-3-yl and the like may be proposed.

R² denotes hydroxy, formyl, -CH_{3-a}F_a, -OCH_{3-a}F_a, amino, CN, halogen, C₁₋₆ alkyl or (CH₂)₁₋₄OH.

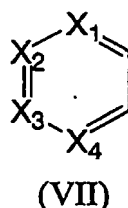
As said R², hydroxy, formyl, -CH_{3-a}F_a (preferably trifluoromethyl), -OCH_{3-a}F_a, halogen, C₁₋₆ alkyl, amino, CN, -(CH₂)₁₋₄OH are preferred, hydroxy, formyl, -CH_{3-a}F_a (preferably trifluoromethyl), -OCH_{3-a}F_a, (preferably trifluoromethoxy), amino, halogen, -C₁₋₆ alkyl, CN or -(CH₂)₁₋₄OH are more preferred and moreover hydroxy, formyl, amino, halogen (preferably fluoro and chloro), -C₁₋₆ alkyl or -(CH₂)₁₋₄OH are still more preferably.

The q denotes an integer of 0-2.

When q is 2, R² may be the same or different.

Provided that, among the compounds represented by formula (I-0), the compounds wherein one of the X₅ is oxygen atom or sulfur atom and the other X₅ is single bond, or both X₅ are single bonds and R¹ is aryl or monocyclic or bicyclic 4-10 membered ring containing 1-4 heteroatoms in the ring which are selected from nitrogen atom, sulfur atom and oxygen atom, (as for the aforesaid R¹, it may be substituted by respectively independently 1-3 of R¹, moreover, when it is aliphatic heterocyclic ring, the aforesaid heterocyclic ring may have 1 or 2 double bonds) are excluded from the compounds of the invention.

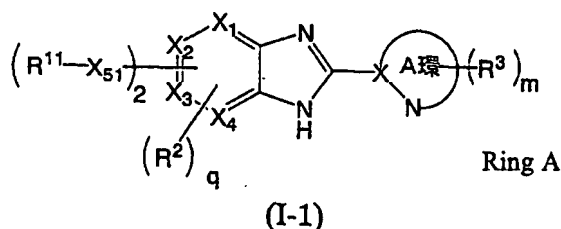
Next, the group represented by formula (VII) which is a partial structure in the said formula (I) will be explained.



X_1 - X_4 in the aforesaid formula (VII) are carbon atoms or nitrogen atoms, and at least 2 among X_1 - X_4 denote carbon atoms.

It is more preferred that all of X_1 - X_4 in the aforesaid formula (VII) are carbon atoms.

Moreover, as preferred form of compounds in accordance with this invention, the case wherein the compound represented by formula (I-0) is represented by formula (I-1)



[wherein, R^{11} denotes a phenyl which may be substituted with 1-3 R^4 , or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4), and also X_{51} denotes $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$, and the other symbols are the same as above] may be proposed.

The "phenyl which may be substituted with 1-3 R^4 " denoted by R^{11} denotes the aforesaid phenyl which may be substituted with 1-3 R^4 .

The "5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring" denoted by R^{11} denotes a group having at least one nitrogen atom in the ring as heterocycle structural atom among the aforesaid 5 or 6 membered monocycle heteroaromatic ring of R^1 , and for example pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and the like may be proposed.

X_1 , X_2 , X_3 and X_4 in formula (I-1) denote the same group of the aforesaid formula (I-0), and preferably all X_1 , X_2 , X_3 and X_4 are carbon atoms.

R^4 in formula (I-1) denotes the same group as R^4 in the said formula (I-0).

X_{51} denotes -O-, -S-, -S(O)- or -SO(O)₂-, and among these, -O- or -S- is preferred, and -O- is more preferred.

Formula (I-1) has 2 groups represented by $-X_{51}-R^{11}$, and these may be the same or different.

As $R^{11}-X_{51}-$ in formula (I-1) (R^{11} may be substituted 1-3 with R^4), for example phenyl sulphonyl, phenoxy, benzyloxy, 2-cyano phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-methylcarbamoyl phenoxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 2-(pyrrolidine-1-carbonyl)-phenoxy, 3-(pyrrolidine-1-carbonyl)-phenoxy, 4-(pyrrolidine-1-carbonyl)-phenoxy, 2-methoxy-phenoxy, 3-methoxyphenoxy, 4-methoxyphenoxy, 2-isopropyl phenoxy, 3-isopropyl phenoxy, 4-isopropyl phenoxy, 2-methylphenoxy, 3-methylphenoxy, 4-methylphenoxy, 2-ethyl phenoxy, 3-ethyl phenoxy, 4-ethyl phenoxy, 2-acetyl phenoxy, 3-acetyl phenoxy, 4-acetyl phenoxy, 2-methanesulphonyl-phenoxy, 3-methanesulphonyl phenoxy, 4-methanesulphonyl phenoxy, 2-methoxycarbonyl phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-ethoxycarbonyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-hydroxyphenoxy, 3-hydroxyphenoxy, 4-hydroxyphenoxy, 2-hydroxymethyl phenoxy, 3-hydroxymethyl phenoxy, 4-hydroxymethyl phenoxy, 2-hydroxyethyl phenoxy, 3-hydroxyethyl phenoxy, 4-hydroxyethyl phenoxy, 2-formyl phenoxy, 3-formyl phenoxy, 4-formyl phenoxy, 2-(1-hydroxyethyl) phenoxy, 3-(1-hydroxyethyl) phenoxy, 4-(1-hydroxyethyl) phenoxy, 2,5-difluoro phenoxy, 2,4-difluoro phenoxy, 2,3-difluoro phenoxy, 2,6-difluoro phenoxy, 2-fluoro phenoxy, 3-fluoro phenoxy, 4-fluoro phenoxy, 2-fluoro-6-carbamoyl phenoxy, 2-difluoromethoxyphenoxy, 3-difluoromethoxyphenoxy, 4-difluoromethoxyphenoxy, 2-trifluoromethoxyphenoxy, 3-trifluoromethoxyphenoxy, 4-trifluoromethoxyphenoxy, 2-cyano-6-fluoro phenoxy, 2-(1H-tetrazol-5-yl) phenoxy, 3-(1H-tetrazol-5-yl) phenoxy, 4-(1H-tetrazol-5-yl) phenoxy, 2-(oxadiazol-3-yl) phenoxy, 3-(oxadiazol-3-yl) phenoxy, 4-(oxadiazol-3-yl) phenoxy, 2-(5-methyl oxadiazol-3-yl) phenoxy, 3-(5-methyl oxadiazol-3-yl) phenoxy, 4-(5-methyl oxadiazol-3-yl) phenoxy, 2-methoxyphenyl sulphonyl, 3-methoxyphenyl sulphonyl, 4-methoxyphenyl sulphonyl, 2-methoxyphenylmethyl sulphonyl, 3-methoxyphenylmethyl sulphonyl, 4-methoxyphenylmethyl sulphonyl,

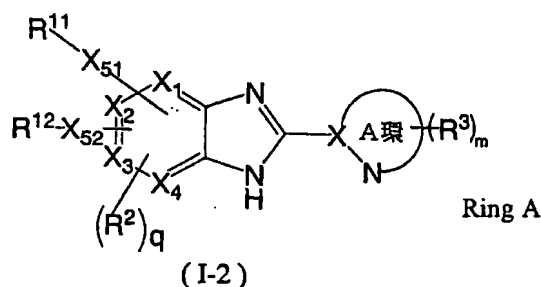
2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-(N-hydroxy amidino) phenoxy, 3-(N-hydroxy amidino) phenoxy, 4-(N-hydroxy amidino) phenoxy, pyridin-2-yl sulphanyl, pyridin-3-yl sulphanyl, pyridin-4-yl sulphanyl, pyridin-2-yloxy, pyridin-3-yloxy, pyridine-4-yloxy, 2-methoxypyridin-3-yloxy, 2-methoxypyridine-4-yloxy, 6-methoxypyridin-3-yloxy, 6-methoxypyridin-2-yloxy, 3-methoxypyridin-2-yloxy, 4-methoxypyridin-2-yloxy, 5-methoxypyridin-2-yloxy, 2-difluoromethoxypyridin-3-yloxy, 6-methylpyridin-2-yl sulphanyl, 5-methylpyridin-2-yl sulphanyl, 4-methylpyridin-2-yl sulphanyl, 3-methylpyridin-2-yl sulphanyl, 4-cyano-pyridin-3-yloxy, 4-dimethylcarbamoyl-pyridin-3-yloxy, 4-methanesulphonyl-pyridin-3-yloxy, 2-cyano-pyridin-3-yloxy, 2-dimethylcarbamoyl-pyridin-3-yloxy, 2-methanesulphonyl-pyridin-3-yloxy, 2-methylpyridin-3-yl sulphanyl, 4-methylpyridin-3-yl sulphanyl, 5-methylpyridin-3-yl sulphanyl, 6-methylpyridin-3-yl sulphanyl, 2-methylpyridin-4-yl sulphanyl, 3-methylpyridin-4-yl sulphanyl, 4-methylpyridin-3-yl sulfonyl, 5-methylpyridin-3-yl sulfonyl, 6-methylpyridin-3-yl sulfonyl, 2-methylpyridin-3-yl sulfonyl, 3-methylpyridin-2-yl sulfonyl, 4-methylpyridin-2-yl sulfonyl, 5-methylpyridin-2-yl sulfonyl, 6-methylpyridin-2-yl sulfonyl, 2-oxo-1,2-dihydropyridin-3-yloxy, 1-methyl-2-oxo-1,2-dihydropyridin-3-yloxy, 1-ethyl-2-oxo-1,2-dihydropyridin-3-yloxy, 1H-imidazol-2-yl sulphanyl, 1-methyl-1H-imidazol-2-yl sulphanyl, 4H-[1,2,4] triazol-3-yl sulphanyl or 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl and the like may be proposed.

As preferred form of the compounds in accordance with this invention, the case wherein both R^{11} in the said formula (I-1) are phenyls which may be substituted by 1-3 of the aforesaid R^4 may be proposed.

Moreover, as preferred form of compound in accordance with this invention, the case wherein both R^{11} in the said formula (I-1) are 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4) may be proposed.

Moreover, as preferred form of compound in accordance with this invention, the case wherein one of R^{11} in the said formula (I-1) is a phenyl which may be substituted by 1-3 of the aforesaid R^4 and the other R^{11} is 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4) may be proposed.

Moreover, as preferred form of compound in accordance with this invention, the case wherein the compound represented by formula (I-0) is formula (I-2)



[wherein, R^{12} denotes 5-7 membered nitrogen-containing heterocycle containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said R^{12} may be substituted with the aforesaid R^4 of 1-3, and moreover when said R^{12} is aliphatic hetero ring, it may contain 1 or 2 double bonds in the ring), and X_{52} is -O-, -S-, -S(O), -S(O)₂- or single bond, and the other symbols are the same as above) may be proposed.

The "4-7 membered nitrogen-containing heterocycle containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, may containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring" denoted by R^{12} denotes 4-7 membered monocyclic heterocycle of the said R1and also a group having at least one nitrogen atom in heterocycle, and for example azetidiny, pyrrolidinyl, piperidinyl, azepanyl, piperazinyl, morpholino, thiomorpholino, homopiperazinyl, imidazolidinyl, pyrazolidinyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl and the like may be proposed.

R^{12} may have 1-3 of the aforesaid R^4 as substituents.

When R^{12} contains 2 or 3 R^4 as substituents, these may be the same or different.

As substituent of R^{12} , among the aforesaid R^4 , -C(O)-C₁₋₆ alkyl of (the said C₁₋₆ alkyl may be substituted with halogen, hydroxy, -N(R⁵¹)R⁵²-, -O-C₁₋₆ alkyl or phenyl), -C(O)-phenyl, -C(O)-C₃₋₇ cycloalkyl, -C(O)-O-C₁₋₆ alkyl, -C(O)-N(R⁵¹)R⁵²-, -C₁₋₆ alkyl, heteroaromatic ring, -S(O)₂-N(R⁵¹)R⁵²-, -S(O)₂-C₁₋₆ alkyl are preferred.

As substituent of R^{12} , for example, acetyl, ethyl carbonyl, propyl carbonyl, isopropyl carbonyl, hydroxyethyl carbonyl, hydroxymethyl carbonyl, methoxymethyl carbonyl, ethoxymethyl carbonyl, methyl, ethyl, phenyl carbonyl, phenethyl carbonyl, benzyl carbonyl, dimethylaminomethyl carbonyl, methylaminomethyl carbonyl, cyclohexyl carbonyl, cyclopentyl carbonyl, 1-methyl-3-oxo butyl carbonyl, methanesulphonyl, ethanesulphonyl, isopropyl sulfonyl, carbamoyl, carbamoylmethyl, carbamoylethyl, pyrrolidine-2-carbonyl, pyrimidinyl, pyrazinyl,

pyridyl, trifluoromethyl carbonyl, 2-hydroxyacetyl, 2-methylamino acetyl, 2-dimethylamino acetyl, 2-ethylamino acetyl, n-propylamino acetyl, isopropyl amino acetyl, oxo, methyl, ethyl, isopropyl and the like may be proposed.

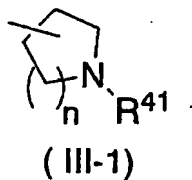
X_{51} in formula (1-2) among the aforesaid X_{51} , -O- or -O- is preferred, and -O- is more preferred.

X_{52} in formula (1-2) denotes -O-, -S-, -S(O)-, -S(O)₂- or single bond.

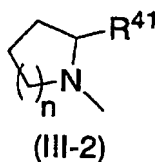
When R^{12} is 4-7 membered saturated nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said nitrogen containing aliphatic hetero ring may be substituted with the aforesaid R^4 of 1-3), X_{52} is preferred to be a single bond.

When R^{12} is 5-7 membered nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, and moreover containing 1 or 2 double bonds in the ring (the said 5-7 membered heterocycle may be substituted with 1-3 of the aforesaid R^4), -O-, -S-, -S(O)- or S(O)₂- is preferred as X_{52} , and -O- is more preferable.

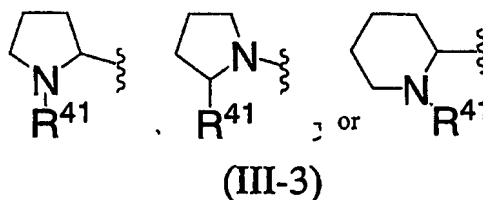
As "4-7 membered saturated nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom" denoted by R^{12} , for example azetidiny, pyrrolidinyl, piperidine, piperidinyl, homo piperidinyl, azepanyl, piperazinyl, morpholino, thiomorpholino, homopiperazinyl, imidazolidinyl, pyrazolidinyl and the like are proposed, and among these, azetidiny, pyrrolidinyl or piperidinyl are preferred, and pyrrolidinyl, piperidinyl, homo piperidinyl are preferred, and the group represented by formula (III-1)



or (III-2)



[wherein, n denotes an integer of 1-3 and R^{41} is the same as aforesaid R^4] is more preferably, and the group by formula (III-3)



[wherein, R^4 denotes the same groups as in the aforesaid definition, and formula (VIII)

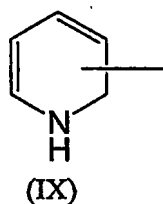


denotes binding site of X_{53}] is still more preferred.

As "4-7 membered saturated nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said nitrogen containing aliphatic hetero ring may be substituted with 1-3 of the aforesaid R^4)" denoted by R^{12} , for example 1-acetyl pyrrolidin-2-yl, 2-acetyl pyrrolidin-1-yl, 1-acetyl-3-fluoro pyrrolidin-2-yl, 1-acetyl-5-methylpyrrolidin-2-yl, 1-acetyl piperidin-2-yl, 1-ethyl carbonyl-pyrrolidin-2-yl, 2-ethyl carbonyl pyrrolidin-1-yl, 1-ethyl carbonyl-piperidin-2-yl, 1-n-propyl carbonyl-pyrrolidin-2-yl, 2-n-propyl carbonyl-pyrrolidin-2-yl, 1-n-propyl carbonyl-piperidin-2-yl, 1-isopropyl-pyrrolidin-2-yl, 2-isopropyl-pyrrolidin-1-yl, 1-isopropyl-piperidin-2-yl, 1-hydroxyethyl carbonyl-pyrrolidin-2-yl, 2-hydroxyethyl carbonyl-pyrrolidin-1-yl, 1-hydroxyethyl carbonyl-piperidin-2-yl, 1-hydroxymethyl carbonyl-pyrrolidin-2-yl, 2-hydroxymethyl carbonyl-pyrrolidin-1-yl, 1-hydroxymethyl carbonyl-piperidin-2-yl, 1-methoxymethyl carbonyl-pyrrolidin-2-yl, 2-methoxymethyl carbonyl-pyrrolidin-1-yl, 1-methoxymethyl carbonyl-piperidin-2-yl, 1-ethoxymethyl carbonyl-pyrrolidin-2-yl, 2-ethoxymethyl carbonyl-pyrrolidin-1-yl, 1-ethoxymethyl carbonyl-piperidin-2-yl, 1-methylpyrrolidin-2-yl, 2-methylpyrrolidin-1-yl, 1-methylpiperidin-2-yl, 1-ethylpyrrolidin-2-yl, 2-ethylpyrrolidin-1-yl, 1-ethylpiperidin-2-yl, 1-phenyl carbonyl-pyrrolidin-2-yl, 2-phenyl carbonyl-pyrrolidin-1-yl, 1-phenyl carbonyl-piperidin-2-yl, 1-phenethyl carbonyl-pyrrolidin-2-yl, 2-phenethyl carbonyl-pyrrolidin-1-yl, 1-phenethyl carbonyl-piperidin-2-yl, 1-benzyl carbonyl-pyrrolidin-2-yl, 2-benzyl carbonyl-pyrrolidin-1-yl, 1-benzyl carbonyl-piperidin-2-yl, 1-dimethylaminomethyl carbonyl-pyrrolidin-2-yl, 2-dimethylaminomethyl carbonyl-pyrrolidin-1-yl, 1-dimethylaminomethyl carbonyl-piperidin-2-yl, 1-methylaminomethyl carbonyl-pyrrolidin-2-yl, 2-methylaminomethyl

carbonyl-pyrrolidin-1-yl, 1-methylaminomethyl carbonyl-piperidin-2-yl, 1-cyclohexyl
 carbonyl-pyrrolidin-2-yl, 2-cyclohexyl carbonyl-pyrrolidin-1-yl, 1-cyclohexyl
 carbonyl-piperidin-2-yl, 1-cyclopentyl carbonyl-pyrrolidin-2-yl, 2-cyclopentyl
 carbonyl-pyrrolidin-1-yl, 1-cyclopentyl carbonyl-piperidin-2-yl, 1-(1-methyl-3-oxobutyl
 carbonyl)-pyrrolidin-2-yl, 2-(1-methyl-3-oxobutyl carbonyl)-pyrrolidin-1-yl,
 1-(1-methyl-3-oxobutyl carbonyl)-piperidin-2-yl, 1-methanesulphonyl-pyrrolidin-2-yl,
 2-methanesulphonyl-pyrrolidin-1-yl, 1-methanesulphonyl-piperidin-2-yl,
 1-ethanesulphonyl-pyrrolidin-2-yl, 2-ethanesulphonyl-pyrrolidin-1-yl,
 1-ethanesulphonyl-piperidin-2-yl, 1-isopropyl sulfonyl-pyrrolidin-2-yl, 2-isopropyl
 sulfonyl-pyrrolidin-1-yl, 1-isopropyl sulfonyl-piperidin-2-yl, 1-carbamoyl-pyrrolidin-2-yl,
 2-carbamoyl-pyrrolidin-1-yl, 1-carbamoyl-piperidin-2-yl, 1-carbamoylmethyl-pyrrolidin-2-yl,
 2-carbamoylmethyl-pyrrolidin-1-yl, 1-carbamoylmethyl-piperidin-2-yl,
 1-carbamoylethyl-pyrrolidin-2-yl, 2-carbamoylethyl-pyrrolidin-1-yl,
 1-carbamoylethyl-piperidin-2-yl, 1-(pyrrolidine-2-ylcarbonyl) pyrrolidin-2-yl,
 2-(pyrrolidine-2-ylcarbonyl) pyrrolidin-1-yl, 1-(pyrrolidine-2-ylcarbonyl)-piperidin-2-yl,
 1-(pyrimidinyl-2-yl) pyrrolidin-2-yl, 2-(pyrimidinyl-2-yl) pyrrolidin-1-yl, 1-(pyrimidinyl-2-yl)
 piperidin-2-yl, 1-(pyrazinyl-2-yl) pyrrolidin-2-yl, 2-(pyrazinyl-2-yl) pyrrolidin-1-yl,
 1-(pyrazinyl-2-yl) piperidin-2-yl, 1-(pyridyl-2-yl) pyrrolidin-2-yl, 2-(pyridyl-2-yl) pyrrolidin-1-yl,
 1-(pyridyl-2-yl) piperidin-2-yl, 1-(pyridyl-3-yl) pyrrolidin-2-yl, 2-(pyridyl-3-yl) pyrrolidin-1-yl,
 1-(pyridyl-3-yl) piperidin-2-yl, 1-trifluoromethyl carbonyl-pyrrolidin-2-yl, 2-trifluoromethyl
 carbonyl-pyrrolidin-1-yl, 1-trifluoromethyl carbonyl-piperidin-2-yl, 1-(2-hydroxyacetyl)
 pyrrolidin-2-yl, 2-(2-hydroxyacetyl) pyrrolidin-1-yl, 1-(2-hydroxyacetyl) piperidin-2-yl,
 1-(2-methylamino acetyl) pyrrolidin-2-yl, 2-(2-methylamino acetyl) pyrrolidin-1-yl,
 1-(2-methylamino acetyl) piperidin-2-yl, 1-(2-dimethylamino acetyl) pyrrolidin-2-yl,
 2-(2-dimethylamino acetyl) pyrrolidin-1-yl, 1-(2-dimethylamino acetyl) piperidin-2-yl,
 1-n-propylamino acetyl-pyrrolidin-2-yl, 2-n-propylamino acetyl-pyrrolidin-1-yl, 1-n-propylamino
 acetyl-piperidin-2-yl, 1-isopropyl-aminoacetyl-pyrrolidin-2-yl, 2-isopropylamino
 acetyl-pyrrolidin-1-yl, 1-isopropylamino acetyl-piperidin-2-yl and the like may be proposed.

As "5-7 membered nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, and moreover containing 1 or 2 double bonds in the ring" denoted by R¹², as embodiments, for example group represented by formula (IX)

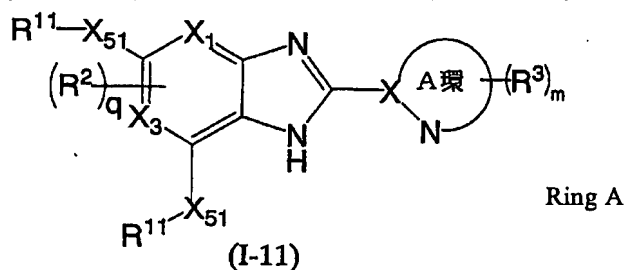


and the like may be proposed.

As "5-7 membered nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, and moreover containing 1 or 2 double bonds in the ring (the said nitrogen-containing aliphatic hetero ring may be substituted with the aforesaid R⁴ of 1-3)" denoted by R¹², as embodiments, for example 1-methyl-2-oxo-1,2-dihydropyridyl, 2-oxo-1,2-dihydropyridyl, 1-ethyl-2-oxo-1,2-dihydropyridyl, 1-isopropyl-2-oxo-1,2-dihydropyridyl, 1-propyl-2-oxo-1,2-dihydropyridyl and the like may be proposed.

Moreover, as R¹¹-X₅₁- in formula (1-2) (R¹¹ may be substituted 1-3 with the aforesaid R⁴), the same groups as in the said formula (I-1) is proposed. Among these, for example, 5-bromopyridin-2-yloxy, 6-methanesulphonyl-pyridin-3-yloxy, 2-chloropyridin-3-yloxy, 4-hydroxy methoxymethyl-phenoxy, 4-methanesulphonyl phenoxy, 6-ethanesulphonyl-pyridin-3-yloxy, 6-cyanopyridin-3-yloxy, 6-acetylamino-pyridin-3-yloxy, 4-methoxymethyl-phenoxy, 4-(2-oxo-2H-pyridine-1-yl) phenoxy, 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yloxy, 2'-fluorobiphenyl-4-yloxy, 6-([1,2,4]-oxadiazol-3-yl) pyridin-3-yloxy, 6-(2-methyl-2H-tetrazol-5-yl)-pyridin-3-yloxy, 4-(2-methyl-2H-tetrazol-5-yl) phenoxy, 6-methoxymethyl-pyridin-3-yloxy, 2-oxo-2H-[1,3'] bipyridine-6'-yloxy, 5-(2-oxo-oxazolidinone-3-yl) pyridin-2-yloxy, 6-methylpyridin-3-yloxy, 6-pyrazin-2-yl pyridin-3-yloxy, 4-acetyl phenoxy and the like are preferred.

As preferred embodiment of the compounds in accordance with this invention, for example, the case that compound represented by the aforesaid formula (I-1) is shown by formula (I-11)



(each symbol is the same as above) may be proposed.

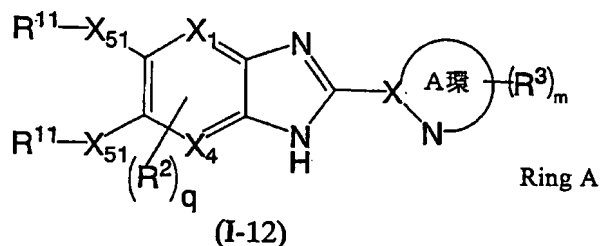
As R^{11} in formula (I-11) (the said R^{11} may be substituted with 1-3 of the aforesaid R^4), the same groups as in R^{11} in the said formula (I-1) may be proposed.

As X_{51} in formula (I-11), -O- or -S- is preferred, and -O- is more preferred.

X_1 and X_3 in formula (I-11) each independently denote carbon atom or nitrogen atom, but the case that both X_1 and X_3 are carbon atoms is preferred.

As $R^{11}-X_{51}-$ in formula (I-11) (said R^{11} may be substituted by the aforesaid R^4 of 1-3), as embodiments, for example, methanesulphonyl phenoxy, 3-methanesulphonyl phenoxy, 2-methoxyphenoxy, 3-methoxyphenoxy, 2-acetyl phenoxy, 3-acetyl phenoxy, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, phenoxy, 2-cyano-6-fluoro phenoxy, 2-methylphenoxy, 3-methylphenoxy, 2-fluoro phenoxy, 3-fluoro phenoxy, 2,3-difluoro phenoxy, 2,4-difluoro phenoxy, 2,5-difluoro phenoxy, 2,6-difluoro phenoxy, pyridin-2-yloxy, pyridin-3-yloxy, 2-methoxypyridin-3-yloxy, 2-difluoromethoxypyridin-3-yloxy and the like are proposed, and among these, 2-methanesulphonyl phenoxy, 2-methoxyphenoxy, 2-acetyl phenoxy, 2-carbamoyl phenoxy, phenoxy, 2-cyano-6-fluoro phenoxy, 2-methylphenoxy, 2-fluoro phenoxy, 2,3-difluoro phenoxy, 2,6-difluoro phenoxy, pyridin-3-yloxy, 2-methoxypyridin-3-yloxy, 2-difluoromethoxypyridin-3-yloxy and the like are preferred.

Moreover, for example, as preferred form of compound in accordance with this invention, the case that compound represented by the aforesaid formula (I-1) is shown by formula (I-12)



(each symbol is the same as above) may be proposed.

R^{11} in formula (I-12) (the said R^{11} may be substituted with the aforesaid R^4 of 1-3), the same groups as in R^{11} in the said formula (I-1) may be proposed.

As X_{51} in formula (I-12), -O- or -S- is preferred, and -O- is more preferred.

X_1 and X_3 in formula (I-12) each independently denote carbon atom or nitrogen atom, but the case that both X_1 and X_3 are carbon atoms is preferred.

As $R^{11}-X_{51}$ - in formula (I-12), in an embodiment for example, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-cyano phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 2-methoxy phenoxy, 3-methoxy phenoxy, 4-methoxy phenoxy, 2-methansulfonyl phenoxy, 3-methansulfonyl phenoxy, 4-methansulfonyl phenoxy, 2-(pyrrolidin-1-carbonyl)-phenoxy, 3-(pyrrolidin-1-carbonyl)-phenoxy, 4-(pyrrolidin-1-carbonyl)-phenoxy, pyridin-2-yloxy, pyridine-3-yloxy, pyridine-4-yloxy, 2-methylcarbamoyl phenoxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 2-(oxazol-3-yl) phenoxy, 2-methoxycarbonyl phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-acetylphenoxy, 3-acetylphenoxy, 4-acetylphenoxy, 2-ethoxycarbonyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-N-hydroxy amidino-phenoxy, 3-N-hydroxy amidino-phenoxy, 4-N-hydroxy amidino-phenoxy, 2-hydroxymethyl-phenoxy, 3-hydroxymethyl-phenoxy, 4-hydroxymethyl-phenoxy, 2-(2H-tetrazol-5-yl) phenoxy, 3-(2H-tetrazol-5-yl) phenoxy, 4-(2H-tetrazol-5-yl) phenoxy, 2-cyano-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 2-carbamoyl-pyridin-3-yl, 2-difluoromethoxy-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yl, 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-formyl phenoxy, 3-formyl phenoxy, 4-formyl phenoxy and the like may be proposed.

Among these, for example, one of $R^{11}-X_{51}$ - is preferred to be 2-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-cyano phenoxy, 4-cyano phenoxy, 2-methoxy phenoxy, 4-methoxy phenoxy, 2-methansulfonyl phenoxy, 4-methansulfonyl phenoxy, pyridin-2-yloxy, pyridin-3-yloxy, pyridin-4-yloxy, 2-cyano-pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 2-carbamoyl-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yloxy, 5-cyano-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 5-carbamoyl-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yloxy, 2-methylcarbamoyl phenoxyoxy, 4-methylcarbamoyl phenoxyoxy, 2-dimethylcarbamoyl phenoxyoxy, 4-dimethylcarbamoyl phenoxyoxy, 2-(oxadiazol-3-yl) phenoxy, 2-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-acetyl phenoxy, 4-acetyl phenoxy, 2-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-N-hydroxyamidino-phenoxy, 4-N-hydroxyamidino-phenoxy, 2-hydroxymethyl-phenoxy, 4-hydroxymethyl-phenoxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-(2H-tetrazol-5-yl) phenoxy, 4-(2H-tetrazol-5-yl) phenoxy, 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-formyl phenoxy, 4-formyl phenoxy and the like, and to be 2-carbamoyl phenoxy, 2-cyano phenoxy, 2-methoxyphenoxy, 2-methanesulphonyl phenoxy, pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 2-(oxadiazol-3-yl) phenoxy, 2-methoxycarbonyl phenoxy,

2-acetyl phenoxy, 2-ethoxycarbonyl phenoxy, 2-N-hydroxy amidino-phenoxy, 2-cyano-pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-carbamoyl-pyridin-3-yloxy, 2-hydroxymethyl-phenoxy, 2-(2H-tetrazol-5-yl) phenoxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-formyl phenoxy and the like is more preferred.

For example, the other R^{11} -X₅₁- is preferred to be 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 3-methoxyphenoxy, 4-methoxyphenoxy, 3-(pyrrolidine-1-carbonyl)-phenoxy, 4-(pyrrolidine-1-carbonyl)-phenoxy, 3-methanesulphonyl phenoxy, 4-methanesulphonyl phenoxy, pyridin-2-yloxy, pyridin-3-yloxy, pyridine-4-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 5-cyano-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 5-carbamoyl-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yloxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 4-(oxadiazol-3-yl) phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 3-acetyl phenoxy, 4-acetyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 3-N-hydroxy amidino-phenoxy, 4-N-hydroxy amidino-phenoxy, 3-hydroxymethyl-phenoxy, 4-hydroxymethyl-phenoxy, 3-(2H-tetrazol-5-yl) phenoxy, 4-(2H-tetrazol-5-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-formyl phenoxy, 4-formyl phenoxy and the like, and to be 4-carbamoyl phenoxy, 4-cyanophenoxy, 4-methoxyphenoxy, 4-methanesulphonyl phenoxy, pyridin-3-yloxy, 4-methylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 4-(oxadiazol-3-yl) phenoxy, 4-methoxycarbonyl phenoxy, 4-acetyl phenoxy, 4-ethoxycarbonyl phenoxy, 4-N-hydroxy amidino-phenoxy, 4-hydroxymethyl-phenoxy, 4-cyano-pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy 4-carbamoyl-pyridin-3-yloxy, 4-(2H-tetrazol-5-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-formyl phenoxy and the like is more preferred.

Moreover, as preferred form of compound in accordance with this invention, compound in accordance with this invention is compound represented by formula (I-0) and the case wherein one of R^1 is phenyl which may be substituted by 1-3 R^4 or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4) and also the other R^1 is 5-7 membered nitrogen-containing heterocycle having at least one nitrogen atom as heteroatom constituted heterocycle, and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, may be proposed.

As said 5-7 membered nitrogen-containing heterocycle, 5 or 6 membered nitrogen-containing

heteroaromatic ring or 5-7 membered nitrogen-containing aliphatic hetero ring may be proposed.

As 5 or 6 membered nitrogen-containing heteroaromatic ring, for example, pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and the like may be proposed.

As the 5-7 membered nitrogen-containing aliphatic heterocycle, for example, azetidiny, pyrrolidinyl, piperidino, piperidinyl, azepanyl, piperazinyl, morpholino, thiomorpholino, homopiperazinyl, imidazolidinyl, pyrazolidinyl and the like may be proposed.

The said heterocycle may be substituted with 1-3 of the aforesaid R^4 , and moreover when said heterocycle is aliphatic hetero ring, it may contain 1 or 2 double bond.

Moreover, as preferred form of compound in accordance with this invention, compound in accordance with this invention is compound represented by formula (I-0) and the case wherein one of R^1 is phenyl which may be substituted by 1-3 R^4 or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted by 1-3 R^4) and also the other R^1 is 5-7 membered nitrogen-containing heteroaromatic ring having at least one nitrogen atom as heteroatom constituted heterocycle, and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, may be proposed.

As 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, the same groups as in an item mentioned above may be proposed.

Moreover, as preferred form of compound in accordance with this invention, compound in accordance with this invention is compound represented by formula (I-0) and the case wherein one of R^1 is phenyl which may be substituted by 1-3 R^4 or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted by 1-3 R^4) and also the other R^1 is 5-7 membered nitrogen-containing aliphatic hetero ring having at least one nitrogen atom as heteroatom constituted heterocycle, and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen containing aliphatic hetero ring may be substituted by 1-3 R^4 , and moreover may contain 1 or 2 double bond in the ring) may be proposed.

Among compound represented by formula (I-0), for example,

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole,
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole,
5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,6-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-cyanopyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-

-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulphonyl-phenoxy)-1H-benzimidazole,
5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
4-(2-fluoro-phenoxy)-2-(pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole,
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole,
4-(2-fluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
4-(2,3-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

le,
4-(2,5-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
1-(2-(6-(5-bromo-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide,
2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile,
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylamino-ethanone,
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,
N-(5-(6-[1-acetyl-pyrrolidin-2-yl]-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide,
1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

N-(2-(2-[6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl]-pyrrolidin-1-yl)-2-oxo-ethyl)-acetamide,
6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • mono trifluoroacetate,
1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridin-2(1H)-one,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
(2-(2-(5-((2'-fluorobiphenyl-4-yl-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine),
6-(1-acetylpyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl] pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(1-acetyl-3-fluoropyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(6'-[methoxymethylpyridin-3-yl] oxy)-2-pyridin-2-yl-1H-benzimidazole,
2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol,
2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide,
5'-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one,
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,
6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-pyrazin-2-ylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetyl-3-fluoropyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)

oxy)-2-pyridin-2-yl-1H-benzimidazole,
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy)
phenyl)-1,3-oxazolidin-2-one,
6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-5-((6-pyrazin-2-ylpyridin-3-yl)
oxy)-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)
oxy)-2-pyrazin-2-yl-1H-benzimidazole,
1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl)
phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzi
midazole,
N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)
pyrrolidin-1-yl)-2-oxo ethanamine,
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl)
oxy)-2-pyrazin-2-yl-1H-benzimidazole,
1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-et
hanone,
1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-
2-yl)-ethanone,
1-(1-(6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-
yl)-ethanone, or
1-(1-(6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrr
olidin-2-yl)-ethanone or pharmacologically acceptable salts thereof and the like may be proposed.

The novel 2-heteroaryl substituted benzimidazole derivatives in accordance with this invention can be present as pharmacologically acceptable salts. As the aforesaid salts, acid addition salt or base addition salt may be proposed.

As for the compounds in accordance with this invention, there are cases that stereoisomers, tautomers or the like such as optical isomers, diastereoisomer, geometric isomer exist according to the type of substituents thereof. Needless to say that these isomers are all included in the compounds in accordance with this invention. Again, needles to say that arbitrary mixture of isomers thereof is included in the compounds in accordance with this invention.

Because the compounds of this invention have glucokinase activation action, the said compounds are useful as a therapeutic agent and/or preventive agent of diabetes mellitus, furthermore as a therapeutic agent and/or preventive agent of diabetic complications.

Wherein, the complications of diabetes mellitus are diseases that occur as a result of the onset of diabetes mellitus, and as the said complications of diabetes mellitus for example, diabetic nephropathy, diabetic retinopathy, diabetic neurosis, diabetic arteriosclerosis and the like are nominated.

Compounds in accordance with this invention can be applicable to both types of diabetes mellitus of insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM)

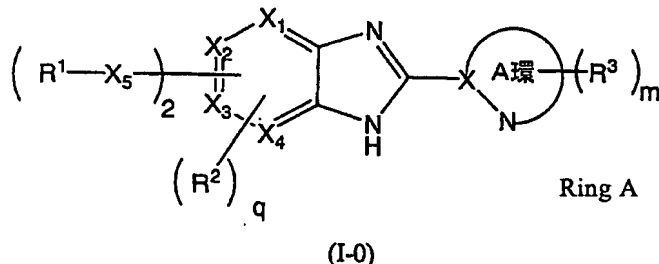
Moreover, the insulin-dependent diabetes mellitus (IDDM) is thought to occur due to predisposition of hereditary insulin secretion lowering and insulin resistance in the skeletal muscle with addition of insulin resistance caused by obesity, and is considered mainly as an adult onset.

The compounds in accordance with this invention are thought to be useful for type II diabetes mellitus that was impossible to achieve satisfactory lowering of blood glucose level with prior art diabetes mellitus drugs, in addition to type I insulin-dependent diabetes mellitus.

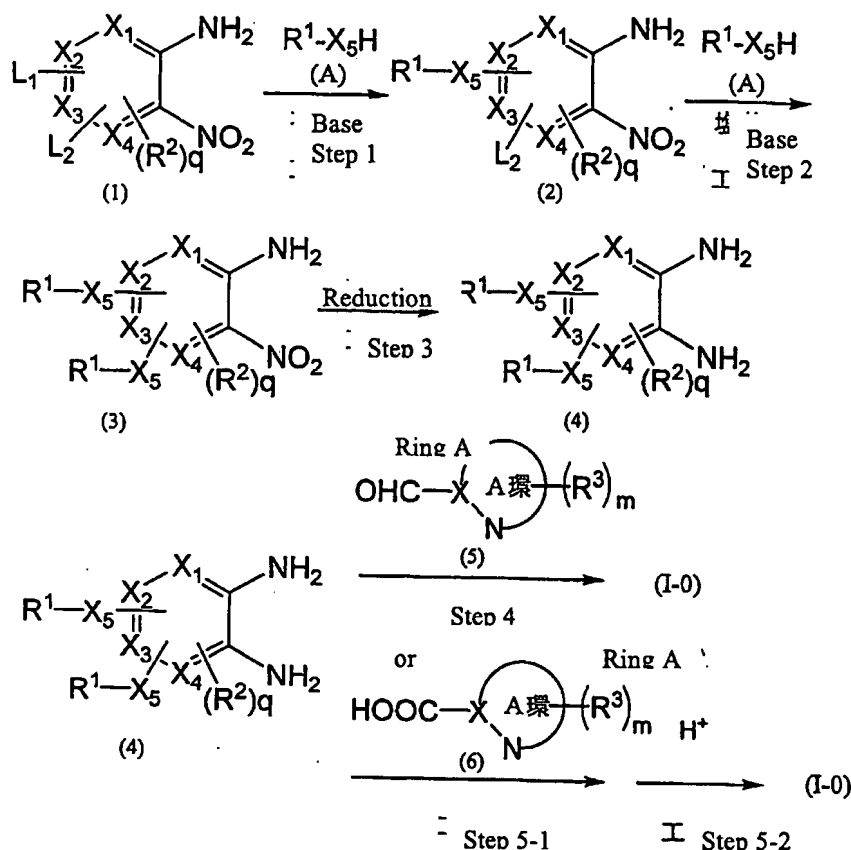
Moreover, in type II diabetes mellitus, it is remarkable that the degree of postprandial hyperglycemia is prolonged compared with healthy person, and the compound in accordance with this invention or pharmacologically acceptable salts thereof are useful for this type II diabetes mellitus.

Moreover, the compounds in accordance with this invention or pharmacologically acceptable salts thereof are useful for the therapy and/or prevention of obesity.

The compound represented by formula (I-0)



(in the formula, each symbol has the same the aforesaid definitions) in accordance with this invention can be produced, for example, using the following process.



(wherein, L^1 and L^2 denote leaving group such as halogen or the like, and each symbol has the same definitions as aforesaid).

(Step 1).

This step is process to produce compound (2) by reacting compound (1) with compound (A) represented by formula R^1-X_5H in the presence of base. More specifically, for example, as L^1 and L^2 , halogen such as fluorine, chlorine and bromine or the like may be proposed. L^1 and L^2 may be the same or different.

As the compound (1) used in this step, for example, 3,5-difluoro-2-nitroaniline, 3,5-dichloro-2-nitroaniline, 3,5-dibromo-2-nitroaniline, 4-bromo-5-fluoro-2-nitroaniline, 4,5-difluoro-2-nitroaniline and the like may be proposed.

Amount of compound (A) used differs depending on compound and kind of solvent, other reaction conditions used, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (1).

Amount of base used differs depending on compound which is used, kind of solvent and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used in this step, any one in which reaction of compound (1) and R_5-X_3H produced compound (2) may be used, but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed. When R_5-X_3H is primary or secondary amine, there does not need to be using base.

As the reaction solvent which is used, it is not restricted in particular so long as it is inert solvent which does not inhibit the reaction, as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is 250 degrees, preferably 0-150 degrees, in this step.

Usually the reaction time is between 0.1-72 hours, preferably from 30 minutes to 5 hours in this step.

Compound (2) obtained in this way can be subjected to next step without being isolated and purified, or after isolation and purification using the like of well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 2).

This step is process to produce compound (3) by reacting compound (2) obtained in the aforesaid step 1 with the same compound (A) as in the aforesaid step 1 or a different compound (A), in the presence of base.

This step can be carried out by the same process as in the aforesaid step 1, a process based on this, or combination of these and the conventional procedure.

(Step 3).

This step is process to produce compound (4) by reducing nitro group of compound (3) obtained in the aforesaid step 2.

As for reductive reaction which is used, process well-known to a person skilled in the art is used in this step.

As the reductive reaction used in this step, as embodiments, for example, catalytic reduction method using hydrogen, formic acid, ammonium formate, hydrazine hydrate and palladium, platinum, nickel catalyst; a reduction method using hydrochloric acid, ammonium chloride and iron, a reduction method using methanol and tin chloride; and the like may be proposed.

Amount of reducing agent used in the aforesaid reductive reaction differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 1-50 equivalents, preferably 2-20 equivalents with respect to 1 equivalent of compound (3).

The reaction solvent which is used is not restricted in particular, so long as there is no hindrance to the reaction, for example methanol, N,N-dimethylformamide, ethyl acetate, tetrahydrofuran and the like and mixed solvent thereof can be used.

The reaction temperature and the reaction time are not restricted in particular. However, it is reacted for about 1-20 hours, preferably 1 to 5 hours approx at the reaction temperature of about -10 to 100°C, preferably around 0-50°C.

Compound (4) obtained in this way can be subjected to next step without being isolated and purified or can be isolated and purified by using the like of well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 4).

This step is process to produce compound (1) by reacting compound (4) obtained in the aforesaid step 3 with compound (5).

In this step cyclisation reaction is carried out by process in accordance with literature (for example, Synthesis, 10 1380-1390 (2000) or the like), or a process based on this, or a combination of these and a conventional procedure.

As compound (5) used, for example, pyridine carboxaldehyde, pyrazine carboxaldehyde, 1H-pyrazole-3-carboxaldehyde and the like may be proposed.

Compound (5) is usually used at 0.1-100 equivalents, preferably 0.1-3 equivalents.

Reaction solvent which is used in this step is not restricted in particular provided it does not hinder the reaction, and for example nitrobenzene, methanol, tetrahydrofuran,

N,N-dimethylformamide, toluene and the like or mixture of these solvents may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is 0.1-72 hours, preferably 0.1 to 24 hours.

Compound (1) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 5-1).

Step 5-1 is process to produce condensed compound by reacting compound (4) obtained in the aforesaid step 3 with compound (6).

Amide reaction in this step is performed using compound (4) and carboxylic acid represented by compound (6) or reactive derivative thereof.

Compound (6) or a reactive derivative thereof is used usually at 0.1-100 equivalents, preferably 0.1-3 equivalents.

As "reactive derivative" of compound (6), for example mixed acid anhydride, active ester, active amide and the like can be nominated, and these can be obtained by process in accordance with for example WO98/05641.

In the aforesaid reaction, when carboxylic acid represented by compound (6) is used, for example carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, diphenyl phosphoryl diazide, dipyridyl disulphide-triphenylphosphine and the like, are preferred and reaction is preferably in the presence of condensing agent such as carbonyldiimidazole and the like.

The quantity of the aforesaid condensing agent used is not limited closely, but usually is 0.1-100 equivalents, preferably 0.1-10 equivalents with respect to compound (6).

Reaction is usually carried out in inert solvent, and, as the aforesaid inert solvent, for example tetrahydrofuran, N,N-dimethylformamide, 1,4-dioxane, benzene, toluene, methylene chloride, chloroform, carbon tetrachloride, 1,2-dichloromethane, pyridine and the like or mixture of these solvents may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is between 0.1-72 hours, preferably from 30 minutes to 24 hours.

Moreover, the aforesaid reaction may be performed in the presence of base and condensation assistant in order that the reaction proceed smoothly.

As base, 4-dimethylaminopyridine, triethylamine and the like may be proposed.

The quantity of the aforesaid base used is 0.1-100 equivalents, preferably 0.1-1 equivalents with respect to 1 mole of carboxylic acid represented by compound (6) or reactive derivative thereof usually.

As condensation assistant, N-hydroxybenzotriazole hydrate, N-hydroxy succinimide and the like may be proposed.

The quantity of the aforesaid condensation assistant used is 1-100 equivalents, preferably 1-5 equivalents with respect to 1 mole of carboxylic acid represented by compound (6) or reactive derivative thereof usually.

In the aforesaid reaction, when amino group or imino group which does not participate in reaction in reaction materials is present, preferably it is suitably protected with protecting group of amino group or imino group, and thereafter, it is reacted, and the aforesaid protecting group of said amino group or imino group is eliminated after reaction.

Condensed compound obtained in this way can be subjected to next step without being isolated and purified or can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 5-2).

Step 5-2 is process to produce compound (I-0) by reacting condensed compound obtained in the aforesaid step 5-1.

In this step cyclisation reaction can be performed by process in accordance with literature (for example, process described in Tetrahedron, Vol 57 Number 9, pp 1793-1800, 2001 or the like) or

a process based on this, or a combination of these and a conventional procedure.

When p-toluenesulfonic acid is used in cyclisation reaction, amount of p-toluenesulfonic acid is usually 0.1-100 equivalents, preferably 0.1-1 equivalents.

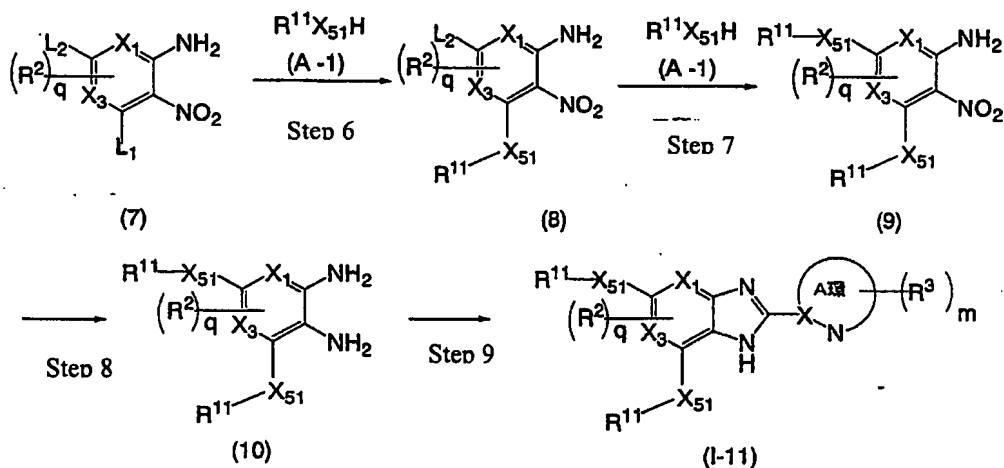
The reaction solvent which is used is not restricted in particular in reaction in this step, provided it does not hinder the reaction, and for example toluene, N,N-dimethylformamide, 1,4-dioxane, N-methylpyrrolidinone and the like or mixture of these solvents may be proposed.

The reaction temperature is 0 to 200 degrees, preferably room temperature to reflux temperature of reaction solvent.

The reaction time is usually 0.1 hours to 72 hours, preferably from 30 minutes to 12 hours.

Compound (I-0) in accordance with this invention obtained in this way may be used without isolation and refinement, or can be isolated and purified by using well-known isolation and separation means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

Compound (I-11) in accordance with this invention can be produced by the following process.



(wherein, L¹, L² denotes leaving group such as halogen or the like; each symbol has the same definitions as aforesaid.

(Step 6).

This step is process to produce compound (8) by reacting compound (7) with compound (A-1) in the presence of base. More specifically, as L¹, L², for example, halogen such as fluorine, chlorine and bromine or the like may be proposed.

Amount of compound (A-1) used differs depending on compound and kind of solvent, other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (7).

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used, in this step, any base which produces compound (8), in reaction of compound (7) and compound (A-1), for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

As the reaction solvent which is used, inert solvent may be proposed, and it is not restricted in particular so long as it does not hinder the reaction. and as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0-250°C in this step.

The reaction time is usually 0.1-72 hours, preferably 0.1-5 hours in this step.

Compound (8) obtained in this way can be subjected to next step without being purified and refined, or it may be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 7).

This step is process to produce compound (9) by reaction of compound (8) with compound (A-1) used in the aforesaid step 1 in the presence of base.

This step can be carried out by the same process as in the aforesaid step 6, a process based on this, or a combination of these processes and conventional procedures.

Compound (9) obtained in this way is isolated and refined using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like, or can be subjected to following step without being purified or being isolated and purified it

(Step 8).

This step is process to produce compound (10) by reducing nitro group of compound (9).

This step can be carried out by the same process as in the aforesaid step 3, a method based on this, or a combination of these with conventional procedures.

Compound (10) obtained in this way can be subjected to next step without being isolated and purified or after isolation and purification using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 9).

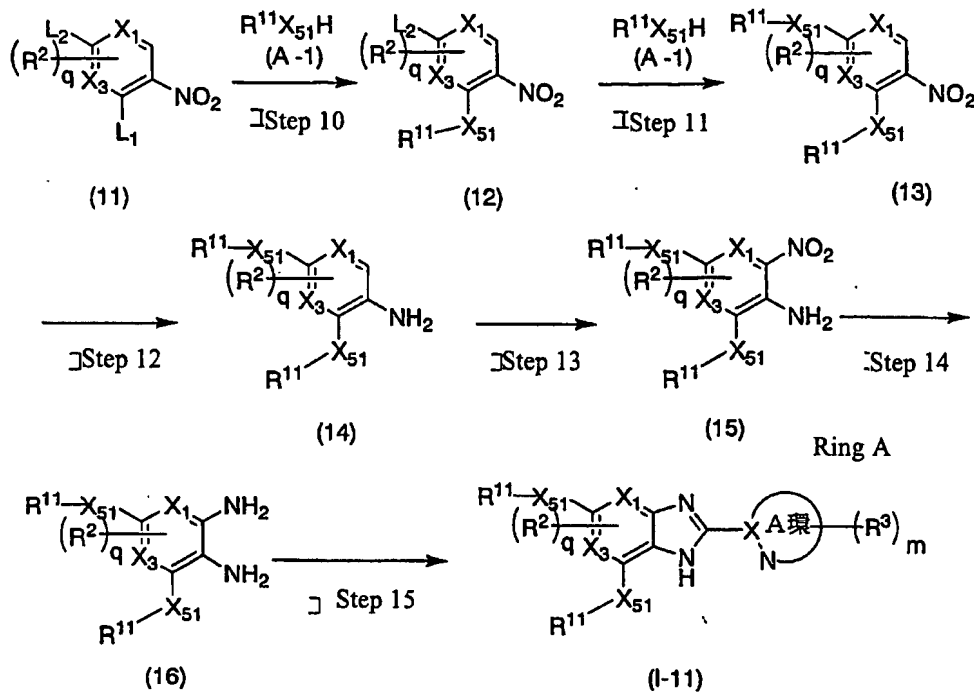
This step is process to produce compound (I-11) in accordance with this invention by reacting compound (10) with aforementioned compound (5) or compound (6).

Reaction of compound (10) and compound (5) can be carried out by the same process as in the aforesaid step 4, a process based on this, or a process combining these and the conventional procedure.

Moreover, reaction of compound (10) and compound (6) can be carried out by the same process as in the aforesaid step 5-1 and 5-2, a process based on this, or a process combining these and the conventional procedure.

Compound (I-11) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Compound (I-11) in accordance with this invention can be produced by the following process.



(wherein, L^1 , L^2 denotes leaving group such as halogen or the like, and each symbol has the same definitions as aforesaid).

(Step 10).

This step is process to produce compound (12) by reaction of compound (11) and aforementioned compound (A-1).

This step can be carried out by the same process as in aforesaid step 6, a process based on this, or a combination of these and a conventional procedure.

Compound (12) obtained in this way can be subjected to next step without being isolated and purified or can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 11).

This step is process to produce compound (13) by reaction of compound (12) and aforementioned compound (A-1).

This step can be carried out by the same process as in aforesaid step 6, a process based on this, or a combination of these and a conventional procedure.

Compound (13) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 12).

This step is process to produce compound (14) by reducing nitro group of compound (13).

This step can be carried out by the same process as in aforesaid step 3, a process based on this, or a combination of these and a conventional procedure.

Compound (14) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 13).

This step is process to produce compound (15) by introducing nitro group into compound (14) obtained in the aforesaid step.

Nitration in this step process may be performed by process in accordance with literature (for example Synthetic Communications Vol. 31 No. 7, pp 1123-1128, 2001 or the like), or a process based on this, or a combination of these and a conventional procedure. If necessary, said nitration reaction is performed with amino groups in compound (14) protected.

When potassium nitrate is used in nitration, amount of potassium nitrate is usually 0.1-100 equivalents, preferably 0.1-2 equivalents.

Reaction solvent which is used is not restricted in particular provided it does not hinder the reaction in this step, and for example trifluoroacetic acid, trifluoroacetic acid anhydride, hydrochloric acid, sulphuric acid, nitric acid and the like may be proposed.

The reaction temperature is usually 0 degrees to reflux temperature of reaction solvent, preferably room temperature to reflex temperature of solvent.

The reaction time is usually 0.1 to 72 hours, preferably from 30 minutes to 12 hours.

Compound (15) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 14).

This step is process to produce compound (16) by reducing the nitro group which compound (15) contains.

This step can be carried out by the same process as in aforesaid step 3, a process based on this, or a combination of these and a conventional procedure.

Compound (16) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 15).

This step is process to produce compound (I-11) in accordance with this invention by reacting compound (16) and aforementioned compound (5) or compound (6).

Reaction of compound (16) and compound (5) can be carried out by the same process as in aforesaid step 4, a process based on this, or a combination of these and a conventional procedure.

Moreover, reaction of compound (16) and compound (6) can be carried out by the same process as in the aforesaid step 5-1 and 5-2, a process based on this, or a process combining these and the conventional procedure.

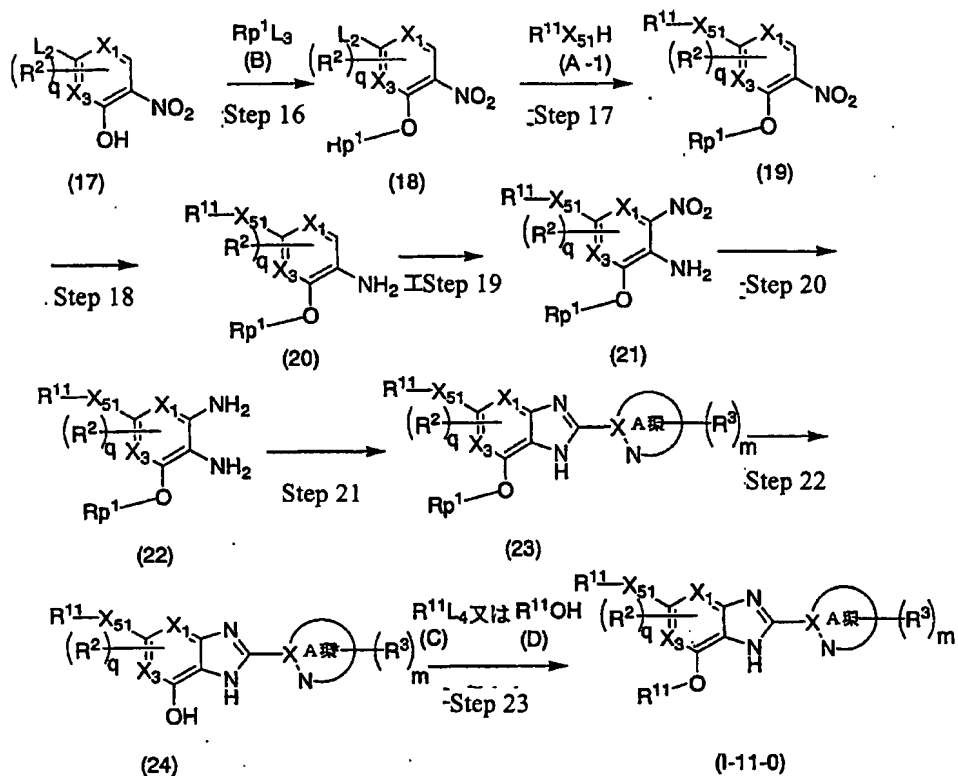
Moreover, it is possible to produce compound (I-11) in accordance with this invention by reacting the aforesaid compound (14) and (6), introducing a nitro group, and finally either reducing said nitro group to amino group, and simultaneously performing cyclisation reaction or carrying out cyclisation separately, in accordance with requirements.

Moreover, amidation, nitration, reduction of nitro group to amine, and cyclisation may be performed by the same method as in step 5-1, step 13, step 3 and step 5-1, a process based on these and a combination of these and a conventional procedure.

Compound (I-11) in accordance with this invention obtained in this way can be isolated and

purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Compound (I-11-0) in accordance with this invention can be produced for example by the following process.



(wherein, L^1, L^2, L^3, L^4 denotes leaving group such as halogen or the like. Rp^1 denotes protecting group of hydroxy. Each symbol has the same definitions as aforesaid).

(Step 16).

This step is reaction to introduce protecting group into compound (17). Introduction of hydroxy protecting group Rp^1 of compound (17) used in this step may be performed as described in the literature, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

More specifically, for example, as Rp^1 , methoxymethyl, methyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethoxymethyl, 2-(trimethylsilyl) ethyl, tert-butyldimethylsilyl, tert-butyl

©Rising Sun Communications Ltd. <http://www.risingsun.co.uk>

carbonyl and the like may be proposed.

Amount of compound (B) used differs depending on compound and kind of solvent, and other reaction conditions used, usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (17).

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used in this step, any one that produces compound (18) in reaction of compound (17) and compound (B) may be used, but for example cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine, imidazole and the like may be proposed.

Reaction temperature is usually 0 – reflux temperature of reaction solvent, and preferably 0-80°C.

Reaction time is usually 0.1-72 hours, and preferably 0.5-12 hours.

As the reaction solvent which is used, inert solvent is proposed, and is not restricted in particular so long as it does not hinder the reaction, as embodiments for example, pyridine, toluene, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (18) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 17).

This step is process to produce compound (19) by reaction compound (18) and the aforesaid compound (A-1).

This step can be carried out by the same process as in aforesaid step 10, a process based on this, or a combination of these and a conventional procedure.

Compound (19) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization,

reprecipitation, chromatography and the like.

(Step 18).

This step is process to produce compound (20) by reducing the nitro group which compound (19) contains.

This step may be performed by the same process as step 12, process based on this, or a combination of these and a conventional procedure.

Compound (20) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 19).

This step introduces nitro group into compound (20) and is process to produce compound (21).

This step can be carried out by the same process as in aforesaid step 13, a process based on this, or a combination of these and a conventional procedure.

Compound (21) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 20).

This step reduces nitro group of compound (21) and is process to produce compound (22).

This step can be carried out by the same process as in aforesaid step 14, a process based on this, or a combination of these and a conventional procedure.

Compound (22) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 21).

This step is process to produce compound (23) by reacting compound (22) with aforementioned

compound (5) or compound (6).

Reaction of compound (22) and compound (5) can be carried out by the same process as in aforesaid step 4, a process based on this, or a combination of these and a conventional procedure.

Moreover, reaction of compound (22) and compound (6) can be carried out by the same process as in the aforesaid step 5-1 and 5-2, a process based on this, or a process combining these and the conventional procedure.

Compound (23) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 22).

This step is process to produce compound (24) by eliminating protecting group of hydroxy of compound (23).

Elimination of hydroxy protecting group Rp^1 of compound (17) used in this step may be performed by the process described in the literature, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991 and the like), a process based on this, or a combination of these and a conventional procedure, and in this step when Rp^1 is benzyl, for example, said elimination of protecting groups can be carried out by using catalytic hydrogenation using palladium-carbon catalyst.

When palladium hydroxide-carbon catalyst is used in removal of Rp^1 , amount of catalyst is usually 0.01-1000 equivalents, preferably 0.1-10 equivalents.

Reaction solvent used in this step is not restricted in particular provided it does not hinder the reaction, for example methanol, ethanol and the like may be proposed.

The reaction temperature is usually room temperature to reflux temperature of reaction solvent, preferably room temperature to 100 degrees.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 12 hours.

Compound (24) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement

means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 23).

This step is process to produce compound (I-2) in accordance with this invention by step of reacting compound (24) and compound (C) (step 23-1) or step of reacting compound (24) and compound (D) (step 23-2).

(Step 23-1).

As L⁴ in compound (C), for example, halogen atom such as chlorine, bromine, iodine or the like may be proposed.

Amount of compound (C) used differs depending on compound and kind of solvent, and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (24).

The reaction in this step is performed in the presence of base. Amount of base used differs depending on compound used, kind of solvent and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (24).

As the base which is used, in reaction of compound (24) and compound (C), any which produced compound (I-2) may be used, but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

As the reaction solvent which is used, inert solvent may be proposed, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0-150°C in this step.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 5 hours in this step.

Compound (I-2) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the

like.

(Step 23-2).

This step is process to produce compound (I-2) in accordance with this invention by reacting compound (24) obtained in the aforesaid step and compound (D) and carrying out protection, deprotection in accordance with requirements.

Reaction of compound (24) and compound (D) can be carried out by so-called Mitsunobu Reaction, in the presence of phosphine compound and azo compound, in accordance with literature (for example Mitsunobu O. et al. "The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products", Synthesis, Vol. 1, 1981 p 1-28), a process based on this or a combination of these with conventional procedure.

Amount of alcohol compound (D) used in this step is usually 0.5-10 equivalents, more preferably 1-3 equivalents with respect to 1 equivalent of compound (24).

As the phosphine compound used in this step, usually for example triphenylphosphine, triethyl phosphine and the like may be proposed.

The amount of phosphine compound used is usually 0.5-10 equivalents, and preferably 1-3 equivalents, for 1 equivalent of compound (24).

As the azo compound which is used, for example diethylazo dicarboxylate, diisopropyl azo dicarboxylate and the like may be proposed.

Amount of azo compound is usually 0.5-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (24).

The reaction time is usually 1-48, preferably 4-12 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 15-30°C in this step.

As the reaction solvent used in this step, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example tetrahydrofuran, toluene and the like may be proposed.

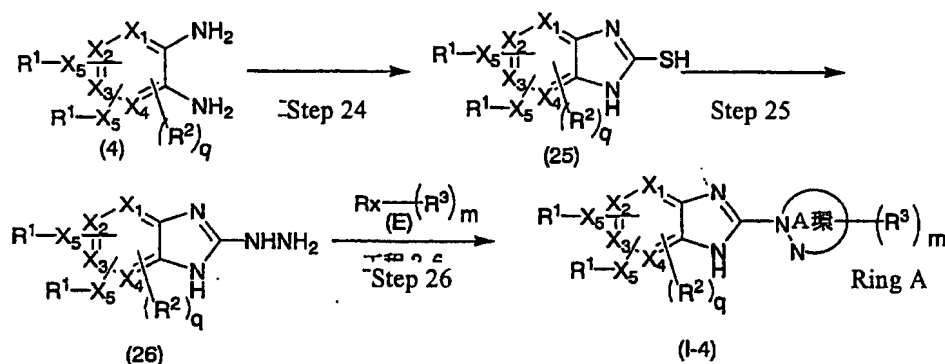
Moreover, it is possible to produce compound (I-11-0) in accordance with this invention by

reacting the aforesaid compound (20) and (6) then introducing a nitro group, and finally, reducing said nitro group to amino group at the same time as it is cyclised, or if necessary, performing cyclisation reaction separately.

Moreover, amidation of compound (20) and compound (6), nitration, nitro group reduction to amino group and cyclisation reaction may be performed by the same processes as in step 5-1, step 13, step 3 and step 5-1, by processes based on these, or on combinations of these and conventional procedures.

Compound (I-11-0) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Of the compounds (I) in accordance with this invention, the compounds (I-4) in which X is nitrogen atom may be produced by the following process.



(wherein, Rx denotes 1-6C alkyl that has 2 halogen atoms, aldehyde, ester, CN or their equivalents, and the other symbols has the same the aforesaid meaning).

(Step 24).

This step is process to produce compound (25) from compound (4).

This reaction may be performed in the presence of base by process in accordance with literature (for example Indian J. Chem. Sect. B, 32, 2;1993, 262-265) or a process based on this, or a combination of these and a conventional procedure.

For example, when it is reacted using sulfur dioxide, amount of the sulfur dioxide which is used

is usually 0.1-500 equivalents, preferably 0.5-10 equivalents.

As the base which is used, in reaction with compound (4), if it is one which produces compound (25), any kind of one may be used, but for example sodium hydroxide, sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

The reaction time is usually 1-48 hours, preferably 4-12 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0 to reflux temperature of solvent in this step.

As the reaction solvent used in this step, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example ethanol, water, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (25) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 25).

This step produces compound (26) using compound (25). Reaction in this step can be performed using hydrazine monohydrate process in accordance with literature (for example, Indian J. Chem. Sect. B, EN, 32, 2;1993, 262-265) or a process based on this, or a combination of these and a conventional procedure.

Amount of the hydrazine monohydrate which is used is usually 0.1-1000 equivalents, preferably 1-100 equivalents.

The reaction time is usually 1-48 hours, preferably 4-24 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0 to reflux temperature of solvent in this step.

Preferably reaction is carried out with absence of solvent in this step, but a reaction solvent may be used provided it does not hinder the reaction, as embodiments of the reaction solvent, for

example ethanol, water, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (26) obtained in this way is isolated and refined by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like, or it can be subjected to following step without being isolated and purified.

(Step 26).

This step is process to produce compound (I-4) in accordance with this invention by reacting compound (26) and compound (E).

Reaction in this step may be performed by process in accordance with literature (for example Indian J. Chem. Sect. B, EN, 32, 2;1993, 262-265 or the like) or a process based on this, or a combination of these and a conventional procedure.

When for example pyrazole is formed, it can be synthesised by carrying out reaction using tetramethoxypropane.

Amount of tetramethoxy propane used is usually 0.1-500 equivalents, preferably 0.5-100 equivalents.

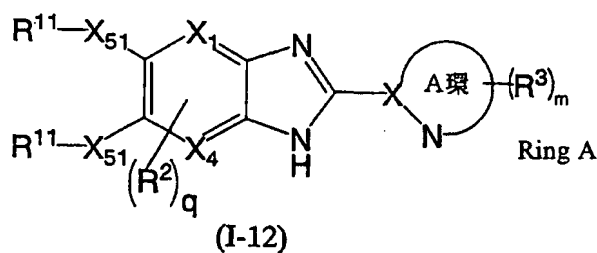
The reaction time is usually 1-48 hours, preferably 4-12 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0 degrees to reflux temperature of solvent in this step.

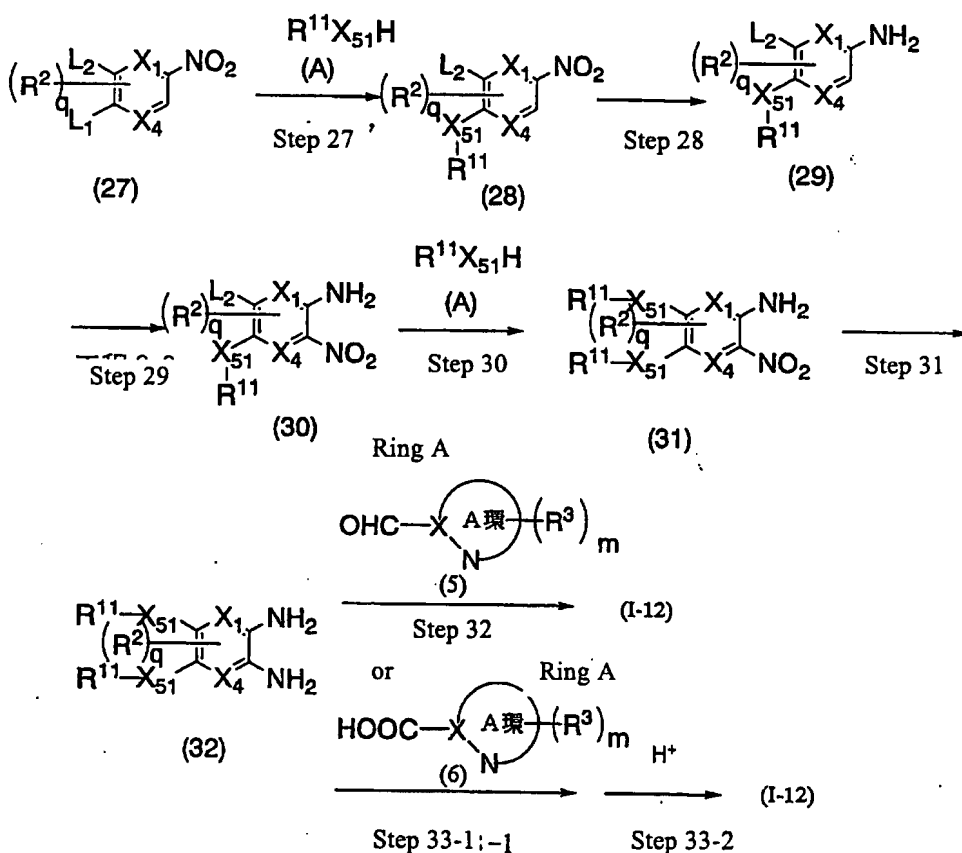
As the reaction solvent used in this step, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example, water, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (I-4) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Compound (I-12) in accordance with this invention represented by



(each symbol is the same as above) may be produced for example by the following process.



(wherein L^1 , L^2 denote a leaving group such as halogen, and the other symbols are same as above).

(Step 27).

This step is process to produce compound (28) by reacting compound (27) and the aforesaid compound (A-1) in the presence of base. As L^1 , L^2 , more specifically, halogen such as fluorine, chlorine and bromine or the like may be proposed.

Amount of compound (A-1) used differs depending on the compound used, the kind of solvent, and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (27).

Amount of base used differs depending on compound used, kind of solvent and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used in this step, if it is one which produces compound (28) by reaction of compound (27) and compound (A-1), any kind may be used, but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

As the reaction solvent which is used, inert solvent may be proposed, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to 150 degrees in this step.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 5 hours in this step.

Compound (28) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 28).

This step is process to produce compound (29) by reducing nitro group of compound (28) obtained in the aforesaid step. As for reductive reaction which is used, process well-known to a person skilled in the art is used in this step.

As the reductive reaction used in this step, as embodiments for example, catalytic reduction method using hydrogen, formic acid, ammonium formate, hydrazine hydrate and palladium, platinum, nickel catalyst, reduction method using methanol and tin chloride, catalytic reduction method using hydrochloric acid, ammonium chloride and iron, and the like may be proposed.

In this step, when 10 % palladium-carbon catalyst is used in reduction of nitro group, amount of 10 % palladium-carbon catalyst is usually 0.01-10 equivalents, more preferably 0.1-1 equivalents.

Reaction solvent which is used is not restricted, provided it does not hinder the reaction in reaction in this step, for example methanol, ethanol, tetrahydrofuran, N,N-dimethylformamide and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 12 hours.

Compound (29) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 29).

This step is process to produce compound (30) by introducing nitro group into compound (29) obtained in the aforesaid step.

Nitration in this step may be performed by process in accordance with literature (for example, Synthetic Communication Vol. 31 issue 7, pp 1123-1128, 2001 or the like), or a process based on this, or a combination of these and a conventional procedure, if necessary after adding protecting group to aniline.

When potassium nitrate is used in nitration, amount of potassium nitrate is usually 0.1-100 equivalents, preferably 0.1-1 equivalents.

Reaction solvent used in this step is not restricted in particular provided it does not hinder the reaction, for example trifluoroacetic acid, trifluoroacetic anhydride, hydrochloric acid, sulphuric acid, nitric acid and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 12 hours.

Compound (30) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 30).

This step is process to produce compound (31) by reacting compound (30) obtained in the aforesaid step and the aforesaid compound (A-1).

This step may be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure, if necessary after adding aniline protecting group.

Compound (31) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 31).

This step is process to produce compound (32) by reducing nitro group of compound (31) obtained in the aforesaid step 30.

The reaction can be carried out by the same process as in aforesaid step 8, a process based on this, or a combination of these and a conventional procedure in this step.

Compound (32) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 32).

This step is process to produce compound (I-2) in accordance with this invention by reacting compound (32) obtained in the aforesaid step 31 and compound (5).

The reaction can be carried out by the same process as in aforesaid step 4, a process based on this, or a combination of these and a conventional procedure in this step.

Compound (I-2) in accordance with this invention obtained in this way can be isolated and

purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 33-1)

This step is process to produce condensed compound by reacting compound (32) obtained by aforesaid step 31 with compound (6).

The reaction can be carried out by the same process as in aforesaid step 5-1, a process based on this, or a combination of these and a conventional procedure in this step.

Condensed compound obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(33-2).

This step is process to produce compound (I-12) in accordance with this invention by cyclization reaction of condensed compound obtained in the aforesaid step 33-1.

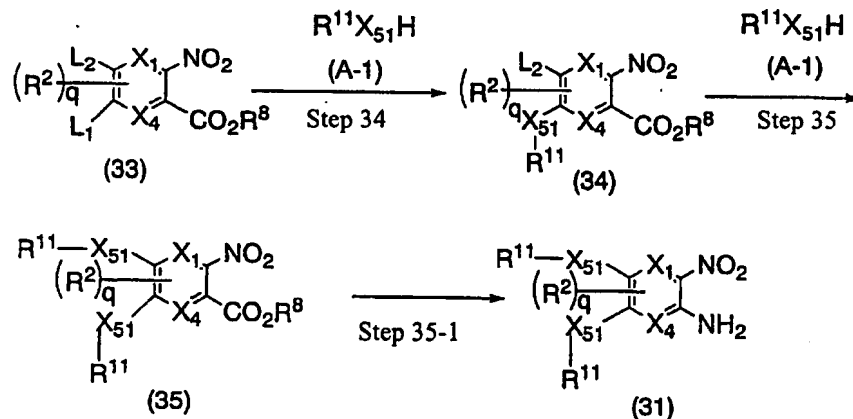
Cyclization reaction can be carried out by the same process as in aforesaid step 5-2, a process based on this, or a combination of these and a conventional procedure in this step.

Moreover, compound (I-11) in accordance with this invention may be produced by reacting the aforesaid compound (29) and (6) then introducing nitro group, and reducing said nitro group to amino group at the same time as cyclization, or if necessary performing cyclization reaction separately, moreover, reacting with compound (A) before cyclization or after cyclization.

Moreover, amidation of compound (29) and compound (6), nitration, reduction of nitro group to amine group, reaction with compound (A) and cyclization reaction may be performed by the same processes as in step 5-1, step 13, step 3, step 30 and step 5-1 respectively, a process based on this or a combination of these processes and the conventional procedure.

Compound (I-12) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Moreover, it is possible to produce compound (I-12) in accordance with this invention by using compound (31) in accordance with the following process.



(wherein, each symbol is the same as above).

(Step 34).

This step is process to produce compound (34) by reacting compound (33) and the aforesaid compound (A-1). In this step, the reaction can be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure.

Compound (34) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 35).

This step is process to produce compound (35) by reacting compound (34) and the aforesaid compound (A-1). In this step, the reaction can be carried out by the same process as in aforesaid step 30, a process based on this, or a combination of these and a conventional procedure.

Compound (35) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 33-1).

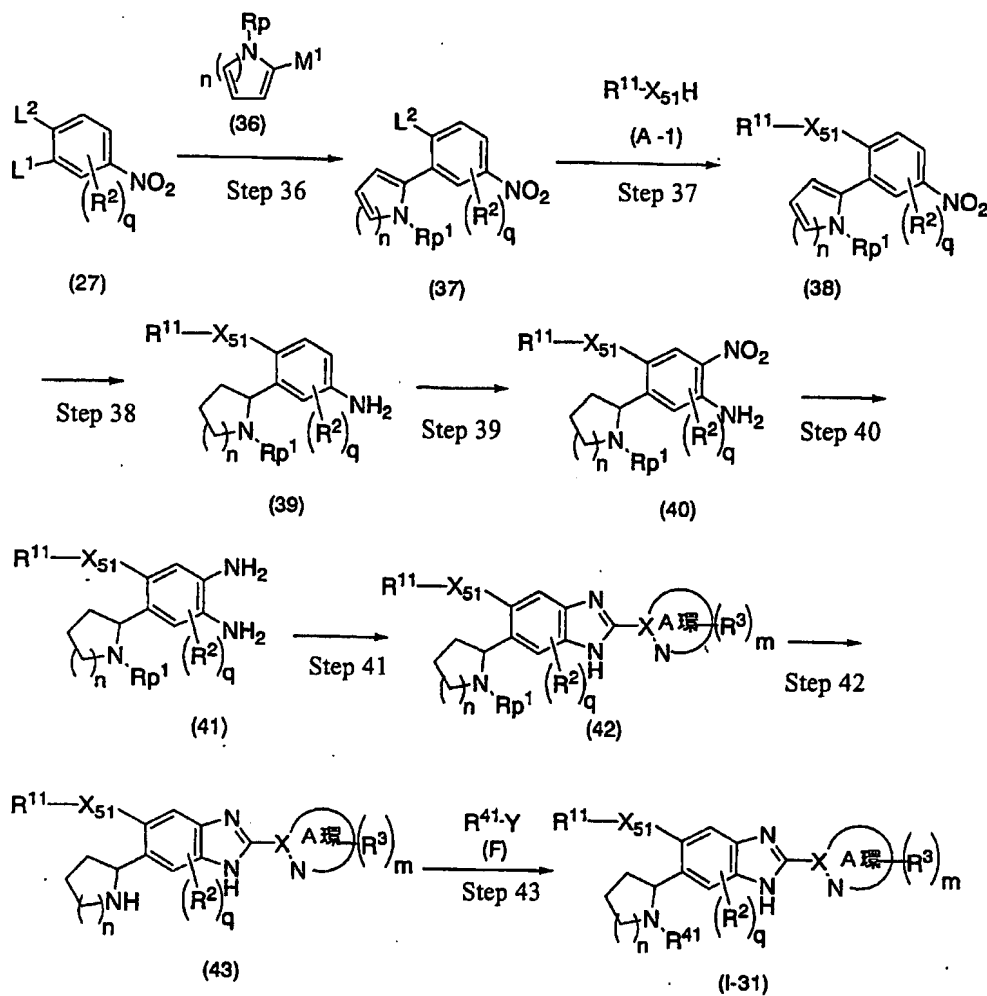
This step is process for producing compound (31) by converted the C(O)OR⁸ of compound (35) obtained in the aforesaid step 35 into amino group, for example so-called Curtius transfer
©Rising Sun Communications Ltd. <http://www.risingsun.co.uk>

reaction may be proposed.

The reaction can be carried out the same process as the step 48 given later, a process based on this or a combination of these processes and the conventional procedure.

Compound (31) obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Using the obtained compound (31), and using the aforesaid step 31, 32, 33-1 or 33-2, compound (I-12) in accordance with this invention may be produced.



(wherein, n denotes 1 or 2, and Y denotes leaving group, and the other symbols are the same as above)

(Step 36)

This step is process for producing compound (37) by reacting the compound (27) mentioned above and compound (36) in the presence of base and metal catalyst.

As L¹ and L², for example, halogen such as fluorine, chlorine, bromine, iodine or the like may be proposed.

Any kind of M¹ may be used as long as it produces compound (37) in the reaction of compound (27) and compound (36), but as embodiments for example tin, boron acid, borate ester and the like trialkyl ester may be proposed. As compound (36), for example, trimethyl-(pyridin-2-yl) tin or 1-(tert butoxycarbonyl) pyrrole-2-boron acid and the like may be proposed.

As compound (36), when trimethyl-(pyridin-2-yl) tin is used, for example, a process using so-called Stille reaction may be proposed.

Moreover, as compound (36), when 1-(tert butoxycarbonyl) pyrrole-2-boron acid is used, for example, a process using so-called Suzuki reaction may be proposed.

Amount of compound (36) used differs depending on the compound and the kind of solvent, other reaction conditions, but it is usually 0.1-50 equivalents with respect to 1 equivalent of compound (27), preferably 0.2-10 equivalents.

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base used in this step, any kind may be used as long as it produces compound (37) in the reaction of compound (27) and compound (36), but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium t-butoxide, triethylamine and the like may be proposed.

Amount of metal catalyst used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.01-10 equivalents, preferably 0.05-5 equivalents.

As metal catalyst used in this step, any type may be used as long as it produces compound (37) in the reaction of compound (27) and compound (36), and for example tetrakis triphenylphosphine palladium, dichloro bis triphenyl phosphine palladium, dichloro (1,1'-bis (dichlorophosphino) ferrocene) palladium or the like may be proposed.

The reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, for example ethylene glycol dimethylether, water, toluene, tetrahydrofuran, N,N-dimethylformamide, 1,4-dioxane, benzene, acetone and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1-72 hours, preferably 30 minutes to 12 hours.

The compound (37) obtained in this way can be subjected to next step without being purified or being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 37).

This step is process for producing compound (38) by reacting compound (37) and the aforesaid compound (A-1).

In this step, the reaction can be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure.

Compound (38) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 38).

This step is process for producing compound (39) by reducing the hetero aromatic ring and nitro group of compound (38) with metal catalyst under hydrogen atmosphere, and in accordance with requirements introducing protecting group.

Amount of reducing agent used is usually 0.01-10 equivalents, preferably 0.1-1 equivalents.

The reducing agent used in this step can be any as long as it produces compound (39) from compound (38), but for example 10 % platinum-carbon, platinum-black or the like may be proposed.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder

the reaction, and for example methanol, ethanol, tetrahydrofuran, 1,4-dioxane, ethyl acetate and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1-72 hours, preferably 0.5-12 hours.

Usually reaction pressure in this step is normal pressure to 100 atmosphere, preferably normal pressure to 20 atmosphere.

Compound (39) obtained in this way can be subjected to next step without being purified or isolated or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 39).

This step is process for producing compound (40) by introducing nitro group into compound (39). The reaction in this step can be carried out by the same method as in the aforesaid step 29 or process based on this, or a combination of these and a conventional procedure. Rp^1 can be converted in accordance with requirements.

Compound (40) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 40).

This step is process for producing compound (41) by reducing the nitro group of compound (40). The reaction in this step can be carried out by the same process as in aforesaid step 31 or process based on this, or a combination of these and a conventional procedure.

Compound (41) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 41).

This step is process for producing compound (42) by reacting compound (41) and the aforesaid compound (5), or for producing compound (42) by reacting compound (41) and the aforesaid compound (6) and thereafter by subjection to cyclization reaction.

Reaction of compound (41) and the aforesaid compound (5) can be carried out by the same process as in aforesaid step 32 or process based on this, or a combination of these and a conventional procedure.

Moreover, the reaction of reacting compound (41) and the aforesaid compound (6), and thereafter subjecting to cyclization reaction, can be carried out by the same process as in the aforesaid step 33-1 and 33-2, a process based on this, or a process combining these and the conventional procedure.

Compound (42) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 42).

This step is for producing compound (43) by removing the protecting group Rp^1 of the amino group of the obtained compound (42).

The process of elimination of the protecting group Rp^1 of amino group can be carried out by the process described above, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

Compound (43) obtained in this way can be subjected to next step without being purified or isolated or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 43).

This step is process to produce compound in accordance with this invention (1-3) by reacting compound (43) and compound (F). Introduction of protecting group R^4 of amino group used in this step may be performed by the process described above (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

As R⁴, for example, alkyl, alkyl amide, carbamoyl, alkylcarbamoyl, alkyl carbamate and the like may be proposed.

As compound (F), for example, acetic anhydride, anhydrous trifluoroacetic acid, propionic acid, chloroacetic acid, acrylic acid ethyl ester, methane sulphonyl chloride, benzyl bromide and the like may be proposed.

Amount of compound (F) used differs depending on the compound used and the kind of solvent, other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (43).

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, and for example dichloromethane, chloroform, tetrahydrofuran, acetonitrile, dimethylformamide, benzene, acetone, ethanol, 2-propanol and the like are nominated.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1 to 72 hours, and preferably from 30 minutes to 12 hours.

Moreover, the aforesaid compound (39) and (6) are reacted, thereafter, nitro group is introduced, and finally cyclisation is carried out simultaneously to the reduction of the said nitro group to amino group, or in accordance with requirements cyclisation reaction is separately carried out, and thereby the compound in accordance with this invention (1-31) can be produced.

Moreover, the amidation of compound (39) and compound (6), nitration and reduction from nitro group to amino group and cyclisation reaction can be carried out respectively by the same process as in the aforesaid step 5-1, step 13, step 3 and step 5-1, processes based on these, or processes combining these and the conventional procedure.

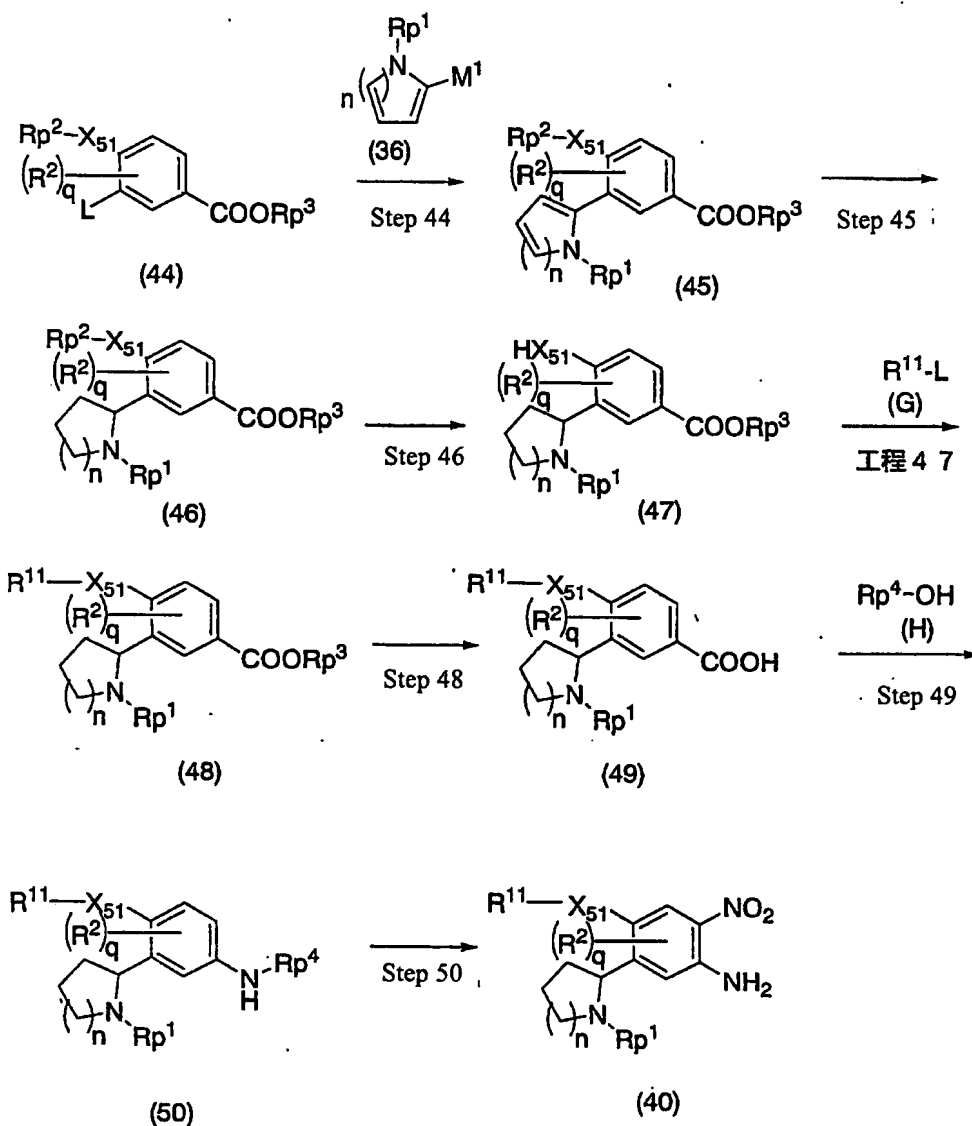
Compound in accordance with this invention obtained in this way (1-31) can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

Moreover, in compound (42), when the protecting group Rp¹ of amino group comes under

desired R^4 , the compound (42) is the compound in accordance with this invention without thereafter carrying out steps 42 and 43.

Moreover, when compound (43) is desired compound, compound (43) comprises compound in accordance with this invention without carrying out step 43.

The compound in accordance with this invention (1-31) can be produced by following process.



(wherein, Rp^2 , Rp^3 and Rp^4 respectively denote protecting group, and L denotes leaving group, and the other symbols are the same as above).

(Step 44).

This step is a processes to produce compound (45) by reacting compound (44) and the aforesaid compound (36). Rp2 denotes protecting group of X₅, and as embodiments for example, methoxymethyl, methyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethoxymethyl, 2-(trimethylsilyl) ethyl, tert-butyldimethylsilyl, tert-butyl carbonyl and the like may be proposed. Moreover, Rp3 denotes protection of carboxyl, and as embodiments for example methoxymethyl, methyl, ethyl, tert-butyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethyl, tert-butyldimethylsilyl and the like may be proposed. Rp4 denotes inert alkyl, and as embodiments for example, methyl, ethyl, tert-butyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethyl and the like may be proposed. The reaction in this step can be carried out by the same process as in aforesaid step 36, a process based on this, or a combination of these and a conventional procedure. Compound (45) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 45).

This step is process for producing compound (46) by reducing the hetero aromatic ring of compound (45) obtained in aforesaid step with metal catalyst under hydrogen atmosphere.

Amount of reducing agent used is usually 0.01-10 equivalents, preferably 0.1-1 equivalents.

The reducing agent used in this step can be any as long as it produces compound (46) from compound (45), but for example 10 % platinum-carbon, platinum-black or the like may be proposed.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, and for example methanol, ethanol, tetrahydrofuran, 1,4-dioxane, ethyl acetate and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1-72 hours, preferably 0.5-12 hours.

Usually reaction pressure in this step is normal pressure to 100 atmosphere, preferably normal pressure to 20 atmosphere.

Compound (46) obtained in this way can be subjected to next step without being purified or isolated or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 46).

This step is process to produce compound (47) by removing the protecting group Rp2 of compound (46). The elimination of the protecting group in this step can be carried out by the process described above, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure. When the Rp2 is methoxymethyl, for example, said elimination of protecting groups can be carried out by using trifluoroacetic acid and the like.

When trifluoroacetic acid is used for the removal of Rp¹, amount of catalyst is usually 0.01-1000 equivalents, preferably 0.1-10 equivalents.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, for example chloroform and the like may be proposed.

Usually the reaction temperature is room temperature to reflux temperature of the reaction solvent, preferably room temperature to 100°C.

Usually the reaction time is 0.1-72 hours, preferably from 30 minutes to 12 hours.

Compound (47) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like. Rp¹ can be converted in accordance with requirements.

(Step 47).

This step is process to produce compound (48) by reacting compound (47) and compound (G). Wherein, L denotes leaving group, and the groups same as in the aforesaid L¹ and L² may be proposed. As compound (G), for example, benzyl bromide, 4-fluoro-benzonitrile, 4-fluoro-benzaldehyde and the like may be proposed. In this step, the reaction can be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure. Compound (48) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known

separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography.

(Step 48).

This step is process to produce compound (49) by removing the protecting group Rp3 of the carboxyl which compound (48). As protecting group of the carboxyl which compound (48), any kind can be used as long as it acts as protecting group of carboxyl in the aforesaid steps 44-47 and it can be readily eliminated in step 48, and for example lower alkyl containing straight chain or branched chain such as methyl, ethyl, tert-butyl and the like, halogeno lower alkyl such as 2-iodo ethyl, 2,2,2-trichloroethyl and the like, allyl lower alkenyl such as 2-propenyl, 2-methyl-2-propenyl and the like, aralkyl and the like such as benzyl, para methoxy-benzyl and the like are nominated.

The introduction and removal process of protecting group Rp3 of such carboxyl can be carried out by the process described in literature (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure. When the Rp2 is methoxymethyl, for example, said elimination of protecting groups can be carried out by using trifluoroacetic acid and the like.

Compound (49) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 49).

This step is process to produce compound (50) by reacting compound (49) and compound (H), and it is so-called Curtius rearrangement reaction and can be carried out using phosphoric acid azide compound in the presence of base and alcohol compound (17-1) process in accordance with literature (for example, Tetrahedron, vol. 31, 1974, pp. 2151-2157 etc), a process based on this, or a combination of these and a conventional procedure.

Amount of alcohol compound (H) used differs depending on the compound and the kind of solvent, other reaction conditions used, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (49).

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the phosphoric acid azide compound used in this step, any kind may be used as long as it produces compound (50) in the reaction of compound (49) and compound (H), but for example diethyl phosphoric acid azide, diphenyl phosphoric acid azide and the like may be proposed.

As the base used in this step, any kind may be used as long as it produces compound (50) in the reaction of compound (49) and compound (H), but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium t-butoxide, triethylamine and the like may be proposed.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, for example toluene, tetrahydrofuran, methylene chloride, chloroform, 1,4-dioxane, benzene and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

Usually the reaction time in this step is 0.1-72 hours, preferably 30 minutes-12 hours.

Compound (50) obtained in this way can be subjected to next step without being purified it made of or isolation to be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 50).

This step is process to produce aforesaid compound (40) by introducing nitro group into compound (50). The reaction in this step can be carried out by the same process as in the aforesaid step 29, a process based on this, or a combination of these and a conventional procedure.

The compound (40) obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like, or without being isolated and purified, and the compound in accordance with this invention (I-3) can be produced by the process of the aforesaid steps 40-43.

Moreover, the amidation of compound (50) and compound (6), nitration and reduction from nitro group to amino group and cyclisation reaction can be carried out respectively by the same process as in the aforesaid step 5-1, step 13, step 3 and step 5-1, processes based on these, or processes

combining these and the conventional procedure. The elimination of Rp4 can be carried out by the process described above, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

The novel 2-heteroaryl substituted benzimidazole derivatives put forward by this invention can exist as pharmacologically acceptable salts, and, the aforesaid salts can be produced in accordance with conventional procedures using the compound (I-0) in accordance with this invention and compounds (I-1), (I-11), (I-12), (I-2), (I-11-0), (I-31), and (I-4) included in compound (I-0).

In an embodiment, when the aforesaid compounds (I-0), (I-1), (I-11), (I-12), (I-2), (I-11-0), (I-31), and (I-4) have basic group originated from amino group, pyridyl group, and the like in the molecule, it can be converted to corresponding pharmacologically acceptable salt by treating the aforesaid compound with acid.

As the aforesaid acid addition salt, the acid addition salts which are for example hydrohalide salt such as hydrochloride, hydrofluoride, hydrobromide, hydroiodide or the like, inorganic salt such as nitrate, perchlorate, sulfate, phosphate, carbonate or the like, lower alkyl sulfonate such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate or the like, aryl sulfonate such as benzenesulphonate, p-toluenesulfonate or the like, organic salt such as fumarate, succinate, citrate, tartrate, oxalate, maleate or the like and amino acid salt or the like such as glutamic acid salt, aspartate or the like may be proposed. Moreover, when the compound of this invention has acidic group in the aforesaid group, when for example carboxyl groups are contained, it can be converted to corresponding pharmacologically acceptable salt by treating the aforesaid compound with base.

As the aforesaid base addition salt, salts with alkali metal salt such as sodium, potassium and the like, alkaline earth metal salt such as calcium, magnesium and the like, ammonium salt, organic base such as guanidine, triethylamine, dicyclohexylamine and the like can be nominated. The compound of this invention may be present as free compound or arbitrary hydrate of salts thereof or solvate furthermore.

For the production of drug for prevention or therapy of type II diabetes mellitus or diseases or symptoms related to this, the compound of formula (I) in accordance with this invention can be combined with carrier substance.

The dosage of the compound of formula (I) in accordance with this invention for the therapy or

prevention of course changes according to the nature of the symptoms to be treated, specific compound selected and administration route.

Moreover, it also changes according to the age, body weight and sensitivity of each patient. Generally, the dosage per day as amount of single administration or a plurality of administrations, it is at least from about 0.001 mg to at most about 100 mg per 1 kg in weight and preferably it is from about 0.01 mg to about 50 mg per 1 kg in weight and is more preferably from about 0.1 mg to 10 mg. There may be a case wherein the dosage exceeding this range may be necessary.

As example of appropriate dose of oral administration, as single dosing or plurality of administrations of 2-4 times per day, it is from at least about 0.01 mg to at most 2.0 g. Preferably, the dose range is, with administration of once or twice per day, from about 1.0 mg to about 200 mg. More preferably, the dose range is from about 10 mg to 100 mg by administration of once per day.

When intravenous administration or oral administration is used, typical administration range is from about 0.001 mg to about 100 mg of compound of formula (I) per 1 kg in weight per day (preferably from 0.01 mg to about 10 mg), and more preferably, from about 0.1 mg to 10 mg of compound of formula (I) per 1 kg in weight per day.

As described earlier, the medicinal composition includes compound of formula (I) and pharmacologically acceptable carrier. The term of "composition" includes, directly or indirectly a product formed by combining, compounding or aggregating two or more components, a product formed as a result of dissociation of one or more components, or a product formed as a results of interaction or other types of action between components, as well as active and inert components that constituting the carrier (including pharmaceutically acceptable excipients).

A composition containing compound of formula (I) in a sufficient dose for therapy, prevention of type II diabetes mellitus or delaying of the onset thereof, in combination with pharmacologically permitted carrier, is preferred.

In order to administer the effective amount of compound in accordance with this invention to mammal, more particularly to human, any appropriate administration route can be used. For example, oral, rectal, local, vein, eye, lung, nose or the like can be used. As example of administrative form, there are tablet, troche, powder, suspension, solution, capsule, cream, aerosol or the like, and the tablet for oral is preferred.

For the preparation of oral composition, any kind of vehicle for ordinary drug can be used, and as

such example, there are for example water, glycol, oil, alcohol, flavor additive, preservation charges, coloring agent or the like. When a liquid composition for oral is prepared, for example suspension, elixir agent and solution are proposed, and as carrier, for example, starch, sugar, microcrystalline cellulose, diluent, granulating agent, lubricant, binding agent, disintegrating agent or the like are proposed, when solid body composition for oral is prepared, for example, powder, capsule, tablet or the like are proposed, wherein the solid body composition for oral is preferred.

From ease of administration, tablet and capsule are the most useful oral administration forms. The tablet can be coated with normal aqueous or non-aqueous technique is possible in accordance with requirements.

In addition to aforesaid usual administration forms, the compound in accordance with formula (1) can be administered by release controlling means and/or delivery apparatus in accordance with U.S. patent number 3,845,770, 3,916,899, 3,536,809, 3,598,123, 3,630,200 and 4,008,719.

The medicinal composition suitable for oral administration in accordance with this invention may be capsule, cachets or tablets containing including active ingredient of pre-determined amount, as powder or granule, or as aqueous solution, non-aqueous liquid, water-in-oil emulsion oil-in-water emulsion, respectively. Such composition may be prepared using any process in pharmaceutics, but in all processes also include a process in which active ingredient and carrier formed from 1 or more essential components are united.

Generally, active ingredient is mixed thoroughly and uniformly with liquid carrier or well-separated solid carrier or both, and thereafter, product is made into a suitable shape in accordance with requirements, and thereby composition is prepared. For example, tablet is prepared by compression and molding, if necessary with 1 or more additional components. Compression tablet is mixed with binding agent, lubricant, inert excipient, surfactant or dispersant in accordance with requirements in a suitable machine and is prepared by compressing active ingredient in shape such as powder and granule or the like freely.

Molded tablet is prepared by forming mixture of moistened compound of powder form and diluent of inert liquid in suitable machine.

Preferably each tablet includes active ingredient in amount of about 1mg to 1g, and each cachet or capsule includes active ingredient in amount of about 1mg to 500 mg.

Example of administrative form of drug of compound of formula (1) is as follows.

Table 1Suspension for injection (I.M.)

Compound of formula (1)	10 mg/ml
Methyl cellulose	5.0 mg/ml
Tween80	0.5 mg/ml
<u>Benzyl alcohol</u>	<u>9.0 mg/ml</u>

Water used for injection is added to make 1.0 ml.

Table 2Tablet

Compound of formula (1)	25 mg/tablet
Methyl cellulose	415 mg/tablet
Tween80	14.0 mg/tablet
<u>Benzyl alcohol</u>	<u>43.5 mg/tablet</u>

Total 500 mg.

Table 3Capsule

Compound of formula (1)	25 mg/capsule
Lactose powder	573.5 mg/capsule
<u>Magnesium stearate</u>	<u>1.5 mg/capsule</u>

Total 600 mg

Table 4Aerosol

Compound of formula (1)	24 mg per container
Lecithin, NF Liq. Conc.	1.2 mg per container
Trichlorofluoromethane, NF	4.025 mg per container
<u>Dichlorodifluoromethane, NF</u>	<u>12.15 mg per container</u>

The compound of formula (1) may be used combined with other agents used not only for disease and symptoms of type 2 diabetes, but also in therapy of onset of 2 type diabetes mellitus, or its prevention or delay. The said other agent may be administered at the same time as compound of formula (1) or separately, by administration route or dose usually used.

When the compound of formula (1) is used at the same time as 1 or more agent, the medicinal composition which included the compound of formula (1) and the other agent is preferable.

Accordingly, medicinal composition in accordance with this invention includes 1 or more other active ingredients in addition to compound of formula (1). Active ingredient used in combination with compound of formula (1), and administered separately or in the same medicinal composition, are not restricted to following examples.

- (a) bisguanide (for example buformin, metformin, phenformin),
- (b) PPAR agonist (for example troglitazone, pioglitazone, rosiglitazone),
- (c) Insulin,
- (d) Somatostatin,
- (e) α -glucosidase inhibitor (for example Voglibose, miglitol, acarbose),
- (f) insulin secretion accelerating agent (for example acetohexamide, carbutamide, chlorpropamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide, glyburide, glyhexamide, glypinamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide, nateglinide, repaglinide), and
- (g) DPP-IV (dipeptidyl peptidase IV) inhibitor.

Weight ratio of compound of formula (1) with respect to 2nd active ingredient varies within wide limits, and moreover, depends on the effective dose of each active ingredient. Accordingly, for example, when compound of formula (1) is used in combination with PPAR agonist, weight ratio with respect to PPAR agonist of compound of formula (1) is generally about 1000:1 – 1:1000 and is preferably about 200:1 – 1:200. The combination of compound of formula (1) and other active ingredient is in the aforesaid range, but in all cases, an effective dose of each active ingredient should be used.

The glucokinase activity which compound represented by compound (1) in accordance with this invention shows, and test process thereof are shown in the following.

The excellent glucokinase activation action that compound represented by the aforesaid formula (1) has can be measured by process in accordance with literature (for example, Diabetes Vol. 5 No. 5, pp1671-1677, 1996) or method in accordance with it.

Glucokinase activity is not measured by measuring glucose-6-phosphoric acid directly, but degree of activation of glucokinase is examined by measuring amount of Thio-NADH produced when glucose-6-phosphoric acid dehydrogenase, which is reporter enzyme, produces phosphogluconolactone from glucose-6-phosphoric acid.

The recombinant human liver used in this assay was expressed in E.coli as FLAG fusion protein and was refined with ANTIFLAG M2 AFFINITY GEL (Sigma).

The assay was carried out at 30°C using flat bottom 96-well plate. 69 µl of assay buffer (25mM Hepes Buffer: pH = 7.2, 2mM MgCl₂, 1mM ATP, 0.5mM TNAD, 1mM dithiothreitol) was discharged, and 1 µl was added of DMSO solution of compound or DMSO control. Thereafter, enzyme mixture (FLAG-GK, 20U/mIG6PDH) 20 µl cooled in ice is discharged, and thereafter, 25 mM glucose 10 µl which is substrate is added, and reaction is started (final glucose concentration = 2.5 mM).

After start of reaction, increase of absorbance of 405 nm was measured every 30 seconds for ten minutes, and the increment during the first five minutes was used, and evaluation of compound was carried out. FLAG-GK was added so that absorbance increment in the presence of 1 % DMSO after five minutes was between 0.05-0.1.

OD was measured at each concentration of the evaluation compound, taking the OD value with DMSO control as 100 %. From OD value of each concentration, E_{max} (%) and EC₅₀ (µM) were calculated, and used as index of GK activation ability of compound.

GK activation ability of compound in accordance with this invention was measured by this method. The results thereof are shown in Table 1 (sic).

Table 5

(GK activation ability of the compounds of this invention)

<u>Compound number</u>	<u>E_{max} (%)</u>	<u>EC₅₀ (µM)</u>
Example 67	832	1.4
Example 26	768	2.3
<u>Example 122</u>	<u>664</u>	<u>1.9</u>

As shown in the aforesaid Table 1, the compounds in accordance with this invention have excellent GK activation ability, using E_{max} and EC₅₀ as index.

Examples

Hereinafter, this invention is described in greater detail by providing examples. However, this invention is not restricted in any way by these.

Preparation Example 1

10 pts. of compound of Production Example 1, heavy magnesium oxide 15 pts. and lactose 75 pts. are uniformly mixed and are made into powder in the form of fine granules or fine powder of 350 micrometer or less. This powder is introduced into capsule container, and capsule is formed.

Preparation Example 2

After uniformly mixing 45 pts. of compound of Production Example 1, starch 15 pts, lactose 16 pts, crystalline cellulose 21 pts, polyvinyl alcohol 3 pts. and distilled water 30 pts, the mixture is pulverised and granulated, and dried, then sieved to make granules of diameter of 1410-177 μm .

Preparation Example 3

Granule is produced by same process as in Preparation Example 2, and thereafter, calcium stearate 3 pts. with respect to this granule 96 pts. is added, and it is compression-molded, and tablet of a diameter of 10 mm is produced.

Preparation Example 4

Crystalline cellulose 10 pts. and calcium stearate 3 pts. are added to 90 pts. of granules obtained by process of Preparation Example 2, and it is compression-molded, and it is formed into tablet of a diameter of 8 mm, thereafter, syrup gelatin - precipitated calcium carbonate mixed suspension is added to this, and sugar coated tablet is produced.

Hereinafter, this invention will be described in greater detail using Preparation Example, Production Example, Reference Example. However, this invention is not restricted in any way by these.

Thin layer chromatograph of the Example used Silicagel60F245(Merck) as plate and UV detector as detection method. Silica gel for as far as column was concerned, and, with WaKogeITM -300C (Wako Jyunyaku), LC-SORBTM SP-B-ODS(Chemco) or YMC-GELTM ODS-AQ120-S50 (Yamamura Institute for Chemical Research) was used as silica gel for reverse phase column.

Meaning of abbreviation in the following Examples is shown below.

i-Bu: isobutyl

n-Bu: n-butyl

t-Bu: t-butyl

Me: methyl

Et: ethyl

Ph: phenyl

i-Pr: isopropyl

n-Pr: n-propyl

CDCl₃: deuterated chloroform

CD₃OD: deuterated methanol

DMSO-d₆: heavy dimethyl sulphoxide

Meaning of abbreviation in nuclear magnetic resonance spectrum is denoted as follows.

s: singlet

d: doublet

dd: double doublet

t: triplet

m: multiplet

br: broad

q: quartet

J: coupling constant

Hz: Hertz.

Example 1

2-pyridine-2-yl-5,6-bis (pyridine-3-yloxy)-1H benzimidazole

Step 1

Synthesis of 3-(2-fluoro-4-nitro-phenoxy)-pyridine

To dimethylformamide 20 ml solution of 3,4-difluoro nitrobenzene 3.18 g were added 3-hydroxypyridine 2.09 g and potassium carbonate 5.52 g, and the reaction liquor was stirred at 90°C for one hour. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1) and the title compound was obtained.

Step 2

Synthesis of 5-fluoro-2-nitro-4-(pyridine-3-yloxy)-phenylamine

To 3-(2-fluoro-4-nitro-phenoxy)-pyridine 4.72 g dissolved in methanol 30 ml, 20 % palladium hydroxide-carbon catalyst 1.0 g was added, and the reaction liquor was stirred under a hydrogen atmosphere for five hours. After eliminating the catalyst by filtration, the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To trifluoroacetic acid 40 ml solution of the obtained crude product was added potassium nitrate 1.88 g, and the reaction liquor was stirred at room temperature overnight, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate.

The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 4/1) and the title compound was obtained.

Step 3Synthesis of 4,5-bis-(pyridine-3-yloxy)-benzene-1,2-diamine

To dimethylformamide 8 ml solution of 3-(2-fluoro-4-nitro-phenoxy)-pyridine 680 mg were added 3-hydroxypyridine 285 mg and potassium carbonate 829 mg, and the reaction liquor was stirred at 90°C for two hours. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate) and the crude product was obtained. To ethanol 10 ml solution of the obtained crude product, developing Raney nickel catalyst 500 mg was added, and the reaction liquor was stirred under a hydrogen atmosphere for two hours. The catalyst was eliminated by filtration, and the title compound was obtained by eliminating the solvent by distillation under reduced pressure.

Step 4Production of 2-pyridine-2-yl-5,6-bis (pyridine-3-yloxy)-1H-benzimidazole

Pyridine-2-carboxaldehyde 0.01 ml was added to nitrobenzene 0.3 ml solution of 4,5-bis-(pyridine-3-yloxy)-benzene-1,2-diamine 30 mg at 120°C, and the reaction liquor was stirred at the same temperature for two hours. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase : water-acetonitrile-0.1% trifluoroacetic acid].

Solvent of the obtained fraction was eliminated by distillation under reduced pressure, and

thereafter, it was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol=20/1), and obtained the title compound as a yellow oily substance.

¹H-NMR (CDCl₃) δ : 7.10-7.40 (4H, m), 7.28 (1H, s), 7.38 (1H, ddd, J = 1.2Hz, 4.8 Hz, 7.6 Hz), 7.62 (1H, s), 7.87 (1H, td, J = 7.6Hz, 1.2 Hz), 8.12-8.40 (4H, m), 8.38 (1H, d, J = 7.6 Hz), 8.63 (1H, d, J = 4.8 Hz), 10.8 (1H, brs).

ESI-MS (m/e): 382 (M+H).

Example 2

5-(2-hydroxymethyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-2-nitro-4-(pyridine-3-yloxy)-phenylamine obtained in Example 1 (Step 2) and 2-hydroxymethyl-phenol, the title compound was obtained as a colourless solid by the same process as in Example 1, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 4.45 (2H, s), 6.76 (1H, d, J = 8.0 Hz), 7.04 (1H, t, J = 6.8 Hz), 7.08-7.30 (5H, m), 7.30-7.43 (2H, m), 7.86 (1H, td, J = 8.0Hz, 2.4 Hz), 8.18-8.32 (1H, m), 8.22 (1H, s), 7.36 (1H, d, J = 7.6 Hz), 8.62 (1H, d, J = 8.4 Hz), 10.54 (1H, brs).

ESI-MS (m/e): 411 (M+H).

Example 3

5-(2-(1-hydroxy-ethyl)-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-(1-hydroxy-ethyl)-phenol, the title compound was obtained as a colourless solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.25-1.34 (6H, m), 4.80-4.96 (1H, m), 7.76 (1H, dd, J = 4.4Hz, 8.0 Hz), 7.02-7.34 (6H, m), 7.38 (1H, t, J = 6.4 Hz), 7.42-7.60 (1H, m), 7.87 (1H, td, J = 7.6Hz, 1.6 Hz), 8.20-8.34 (2H, m), 8.39 (1H, d, J = 7.6 Hz), 8.60-8.64 (1H, m), 10.72 (1H, brs).

ESI-MS (m/e): 425 (M+H).

Example 4

5-(2-acetyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-acetyl-phenol, the title compound was obtained as colourless solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.22-2.50 (3H, m), 6.81 (1H, d, J = 8.4 Hz), 7.00-7.45 (4H, m), 7.45-7.95 (5H, m), 8.20-8.35 (2H, m), 8.37 (1H, d, J = 7.6 Hz), 8.60-8.70/(1H, m), 10.49 (1H, brs).

ESI-MS (m/e): 423 (M+H).

Example 5

5-(2-cyano-phenoxy)--2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-hydroxy-benzonitrile, the title compound was obtained as a straw-coloured solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.80 (1H, t, J = 8.0 Hz), 7.06 (1H, t, J = 7.6 Hz), 7.25-7.35 (2H, m), 7.35-7.7471H, m), 7.56 (1H, d, J = 7.6 Hz), 7.58-7.70 (1H, m), 7.87 (1H, t, J = 7.6 Hz), 8.12-8.25 (1H, m), 8.31 (1H, brs), 8.38 (1H, d, J = 8.0 Hz), 8.58-8.68 (1H, m), 10.80-11.08 (1H, m).

ESI-MS (m/e): 406 (M+H).

Example 65-(3-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-hydroxy-benzonitrile, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 7.02-7.08 (2H, m), 7.14 (1H, d, J = 7.5 Hz), 7.20 (1H, dd, J = 4.4Hz, 7.5 Hz), 7.28-7.36 (3H, m), 7.39 (1H, t, J = 5.9 Hz), 7.42-7.52 (1H, m), 7.88 (1H, dt, J = 1.6Hz, 7.9 Hz), 8.22 (1H, d, J = 3.6 Hz), 8.30 (1H, d, J = 3.6 Hz), 8.39 (1H, d, J = 7.9 Hz), 8.62 (1H, d, J = 5.9 Hz).

ESI-MS (m/e): 406 (M+H).

Example 75-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-hydroxy-benzonitrile, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.84 (2H, d, J = 7.0 Hz), 7.04-7.12 (1H, m), 7.12-7.26 (1H, m), 7.26-7.43 (1H, m), 7.30-7.43 (1H, m), 7.51 (2H, d, J = 7.0 Hz), 7.44-7.76 (1H, m), 7.78-7.90 (1H, m), 8.12-8.21 (1H, m), 8.21-8.30 (1H, m), 8.30-8.40 (1H, m), 8.43-8.65 (1H, m), 10.88 (1H, brs).

ESI-MS (m/e): 406 (M+H).

Example 85-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-hydroxy-benzoic acid dimethyl amide, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.00 (3H, brs), 3.08 (3H, brs), 6.83 (1H, d, J = 8.8 Hz), 6.86 (1H, d, J = 8.8 Hz), 7.18-7.23 (2H, m), 7.26-7.36 (3H, m), 7.38-7.42 (1H, in), 7.61 (1H, d, J = 2.5 Hz), 7.89 (1H, dd, J = 7.7, 7.7 Hz), 8.19-8.38 (2H, m), 8.36 (1H, d, J = 7.7 Hz), 8.63 (1H, d, J = 4.8 Hz)

ESI-MS (m/e): 452 (M+H).

Example 9**5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 4-methanesulphonyl-phenol, the title compound was obtained by the same method as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.40 (3H, s), 6.96 (2H, d, J = 8.8 Hz), 7.10-7.16 (1H, m), 7.17-7.25 (1H, m), 7.32 (1/2H, s), 7.38, (1/2H, s), 7.39-7.43 (1H, m), 7.65 (1/2H, s), 7.70 (1/2H, s), 7.83 (2H, dd, J = 8.8, 3.1 Hz), 7.90 (1H, ddd, J = 7.8, 7.8, 1.7 Hz), 8.23 (1H, brs), 8.32 (1H, brs), 8.39 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 4.7 Hz), 10.84 (1H, brs).

ESI-MS (m/e): 459 (M+H).

Example 10**5-(4-methoxycarbonyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 4-hydroxy-benzoic acid methyl ester, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.88 (3H, s), 6.82 (2H, d, J = 8.8 Hz), 7.12 (1H, ddd, J = 8.6, 2.9, 1.5 Hz), 7.18 (1H, dd, J = 8.6, 4.8 Hz), 7.28 (1H, brs), 7.32 (1H, brs), 7.87 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 7.92 (2H, d, J = 8-8 Hz), 8.20 (1H, d, J = 2.9 Hz), 8.27 (1H, d, J = 4.8 Hz), 8.37 (1H, dd, J = 7.7, 1.1 Hz), 8.61 (1H, dd, J = 5.1, 1.8 Hz), 10.80 (1H, brs)

ESI-MS (m/e): 439 (M+H).

Example 11**5-(2-formyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 2-hydroxy-benzaldehyde, the title compound was obtained as a straw-coloured solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.80 (1H, d, J = 8.4 Hz), 6.92-7.58 (6H, m), 7.83 (1H, d, J = 8.0 Hz), 7.87 (1H, td, J = 7.6Hz, 1.2 Hz), 8.12-8.34 (3H, m), 8.39 (1H, d, J = 8.4 Hz), 8.55-8.67 (1H, m), 10.06 (1H, s)

ESI-MS (m/e): 409 (M+H).

Example 12**5-(2-carboxy-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 2-hydroxybenzoic acid, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 6.83 (2H, d, J = 8.8 Hz), 7.31 (1H, ddd, J = 8.6, 2.9, 1.5 Hz), 7.34 (1H, ddd, J = 8.6, 4.8, 0.7 Hz), 7.48 (1H, dd, J = 7.7, 4.8 Hz), 7.54 (1H, s), 7.56 (1H, s), 7.92 (2H, d, J = 8.8 Hz), 7.96 (1H, ddd, J = 7.7, 7.7, 1.5 Hz), 8.9 (1H, dd, J = 2.9, 0.7 Hz), 8.20 (1H, dd, J = 4.8,

1.5 Hz), 8.27 (1H, d, J = 7.7 Hz), 8.72 (1H, d, J = 4.8 Hz).

ESI-MS (m/e): 425 (M+H).

Example 13

5-(2-methyl-pyridin-5-yl sulphanyl)-2-pyridine-2-yl- 6-(pyridine-3- yloxy)-1H- benzimidazole

Using 6-methyl-pyridine-3-thiol, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.53 (3H, s), 7.05 (1H, d, J = 7.6 Hz), 7.05, 7.36 (tautomer, 1H, s), 7.12-7.24 (2H, m), 7.32-7.36 (1H, m), 7.44, 7.76 (tautomer, 1H, s), 7.50-7.56 (1H, m), 7.83 (1H, t, J = 8.0 Hz), 8.26-8.36 (3H, m), 8.45 (1H, s), 8.56 (1H, d, J = 4.4 Hz), 11.28-11.40, 11.40-11.50 (tautomer, 1H, brs).

ESI-MS (m/e): 412 (M+H).

Example 14

5-(2-ethoxycarbonyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H- benzimidazole

4-methanesulphonyl-phenol and 2-hydroxybenzoic acid ethyl ester were successively used, and, by the same process as in Example 1, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 1.19 (3H, t, J = 7.0 Hz), 3.03 (3H, s), 4.14 (2H, q, J = 7.0 Hz), 6.87 (1H, dd, J = 7.4, 6.3 Hz), 7.00 (2H, dd, J = 9.0, 2.2 Hz), 7.10-7.17 (1H, m), 7.14 (1/2H, brs), 7.32 (1/2H, brs), 7.37-7.43 (2H, m) 7.49 (1/2H, brs), 7.67 (1/2H, brs), 7.81 (2H, dd, J = 9.0, 2.2 Hz), 7.82-7.90 (2H, m), 8.36-8.40 (1H, m), 8.62-8.64 (1H, m), 10.85 (1H, brs).

ESI-MS (m/e): 530 (M+H).

Example 15

5-(2-dimethylcarbamoyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H- benzimidazole

4-fluoro-5-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 2-hydroxybenzoic acid dimethyl amide were successively used, and, by the same process as in Example 14, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 2.58-3.06 (9H, m), 6.83 (1/3H, d, J = 8.6 Hz), 6.86 (2/3H, d, J = 8.4 Hz), 7.02-7.11 (3H, m), 7.12-7.18 (2H, m), 7.12-7.18 (1/2H, m), 7.23-7.33 (1H, m), 7.23-7.33 (1/2H, m), 7.36-7.40 (1H, m), 7.58 (1/3H, s), 7.64 (2/3H, s), 7.83-7.90 (3H, m), 8.34-8.38 (1H, m), 8.62-8.64 (1H, m), 10.58 (2/3H, brs), 10.61 (1/3H, brs)

ESI-MS (m/e): 529 (M+H).

Example 165-(2-methoxy-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-methoxy-phenol, the title compound was obtained by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.03 (3H, s), 3.69 (3H, s), 6.87-6.95 (3H, m), 7.00 (1/2H, s), 7.08 (2H, dd, J = 8.9, 2.8 Hz), 7.08-7.38 (1H, m), 7.31 (1/2H, s), 7.35 (1/2H, s), 7.35-7.38 (1H, m), 7.64 (1/2H, s), 7.83 (2H, dd, J = 8.9, 2.8 Hz), 7.87 (1H, dd, J = 7.8, 1.6 Hz), 8.33-8.38 (1H, m), 8.60-8.62 (1H, m), 10.62 (1/2H, brs), 10.73 (1/2H, brs).

ESI-MS (m/e): 488 (M+H).

Example 175-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 2-hydroxy-benzonitrile, the title compound was obtained as a colourless solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.78 (1H, d, J = 8.4 Hz), 6.86 (2H, t, J = 9.6 Hz), 7.09 (1H, dd, J = 8.4 Hz, 12.8 Hz), 7.37-7.55 (4H, m), 7.62-7.92 (4H, m), 8.40 (1H, d, J = 8.4 Hz), 8.64 (1H, d, J = 4.0 Hz).

ESI-MS (m/e): 483 (M+H).

Example 185-(4-dimethylcarbamoyl-phenoxy)-6-phenoxy-2-pyridine-2-yl-1H-benzimidazole

4-hydroxybenzoic acid dimethyl amide and phenol were successively used, and, by the same process as in Example 1, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 2.99 (3H, brs), 3.07 (3H, brs), 6.85-6.88 (4H, m), 6.97-7.14 (1H, m), 7.21-7.27 (3H, m), 7.31-7.37 (3H, m), 7.55 (1/2H, brs), 7.61 (1/2H, brs), 7.84 (1H, ddd, J = 7.7, 7.7, 1.5 Hz), 8.35 (1H, d, J = 7.7 Hz), 8.61 (1H, brs), 10.48 (1/2H, brs), 10.51 (1/2H, brs).

ESI-MS (m/e): 451 (M+H).

Example 195-(4-dimethylcarbamoyl-phenoxy)-6-(4-methylsulfanyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-fluoro-5-(4-dimethylcarbamoyl-phenoxy)-2-nitro-phenylamine obtained in Example 18 and 4-methylmercapto-phenol, the title compound was obtained by the same process as in Example 1, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.44 (3H, s), 2.99 (3H, brs), 3.07 (3H, brs), 6.81 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 7.18 (2H, d).

ESI-MS (m/e): 497 (M+H).

Example 20

5-(4-dimethylcarbamoyl-phenoxy)-6-(2-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-methanesulphonyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.94 (3/2H, s), 2.99 (3H, brs), 3.03 (3/2H, brs), 3.08 (3H, brs), 6.88-6.93 (3H, m), 7.15-7.22 (1H, m), 7.24 (1/2H, s), 7.34-7.42 (3H, m), 7.39 (1/2H, s), 7.45-7.52 (1H, m), 7.64 (1/2H, s), 7.70 (1/2H, s), 7.86-7.90 (1H, m), 8.00 (1H, d, J = 7.8 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 3.9 Hz), 10.72 (1H, brs).

ESI-MS (m/e): 529 (M+H).

Example 21

5-(4-dimethylcarbamoyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-methanesulphonyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.00 (3H, brs), 3.03 (3H, s), 3.08 (3H, brs), 6.81 (2H, d, J = 8.1 Hz), 6.95 (2H, d, J = 8.4 Hz), 7.26 (1/2H, brs), 7.32 (2H, d, J = 8.1 Hz), 7.39 (1H, dd, J = 7.7, 4.9 Hz), 7.64 (1/2H, brs), 7.66 (1/2H, brs), 7.79 (2H, d, J = 8.4 Hz), 7.87 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 8.37 (1H, d, J = 7.7 Hz), 8.63 (1H, d, J = 4.9 Hz), 10.77 (1H, brs).

ESI-MS (m/e): 529 (M+H).

Example 22

5-(4-dimethylcarbamoyl-phenoxy)-6-(4-methoxy-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-methoxy-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.00-3.07 (6H, m), 3.76 (3/2H, s), 3.77 (3/2H, s), 6.74-6.86 (4H, m), 6.91 (2H, d, J = 8.4 Hz), 7.05 (1/2H, brs), 7.19 (1/2H, brs), 7.32-7.36 (1H, m), 7.35 (2H, d, J = 8.4 Hz), 7.43 (1/2H, brs), 7.58 (1/2H, brs), 7.83 (1H, dd, J = 7.7, 7.7 Hz), 8.33 (1H, dd, J = 7.7, 3.17 Hz), 8.58-8.61 (1H, m), 10.58 (1/2H, brs), 10.79 (1/2H, brs).

ESI-MS (m/e): 481 (M+H).

Example 23

5-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-2-yloxy)-1H-benzimidazole ditrifluoroacetic acid salt

Using 2-hydroxypyridine, the title compound was obtained as yellow solid by the same process

as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 6.93-7.13 (4H, m), 7.37-7.45 (2H, m), 7.41 (1Hx1/2, s), 7.56 (1Hx1/2, s), 7.64 (1Hx1/2, s), 7.67-7.75 (1H, m), 7.77-7.84 (1H, m), 7.81 (1Hx1/2, s), 8.02-8.06 (1H, m), 8.12-8.20 (1H, m), 8.27-8.33 (1H, m), 8.82-8.87 (1H, m).

ESI-MS (m/e): 452 (M+H).

Example 24

5-(4-dimethylcarbamoyl-phenoxy)-6-(2-ethoxycarbonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-hydroxybenzoic acid ethyl ester, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.20 (3H, t, J = 7.0 Hz), 3.01 (3H, brs), 3.07 (3H, brs), 4.17 (2H, q, J = 7.0 Hz), 6.80-6.91 (3H, m), 7.08-7.14 (1H, m), 7.12 (1/2H, brs), 7.18 (1/2H, brs), 7.26-7.41 (4H, m), 7.49 (1/2H, brs), 7.61 (1/2H, brs), 7.84-7.87 (2H, m), 8.34-8.38 (1H, m), 8.61-8.62 (1H, m), 10.85 (1/2H, brs), 10.95 (1/2H, brs).

ESI-MS (m/e): 523 (M+H).

Example 25

5-(2-dimethylcarbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-hydroxybenzoic acid dimethyl amide, the title compound was obtained as straw-coloured solid by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.64-3.08 (12H, m), 6.81 (1/2H, s), 6.85 (1/2H, s), 6.94 (1H, dd, J = 8.8, 2.7 Hz), 7.08 (1/2H, s), 7.12 (1/2H, s), 7.21 (1/2H, s), 7.24 (1/2H, s), 7.25-7.29 (2H, m), 7.30-7.34 (1H, m), 7.35-7.53 (2H, m), 7.59 (1H, d, J = 3.1 Hz), 7.83-7.88 (1H, m), 8.33-8.38 (1H, m), 8.63 (1H, d, J = 4.9 Hz), 10.52 (1H, brs)

ESI-MS (m/e): 522 (M+H).

Example 26

5-(2-acetyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-acetyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.36 (3/2H, s), 2.40 (3/2H, s), 3.00 (3H, brs), 3.08 (3H, brs), 6.76-6.84 (3H, m), 7.05-7.11 (1H, m), 7.15-7.25 (1H, m), 7.26-7.28 (1H, m), 7.32-7.35 (2H, m), 7.38-7.42 (1H, m), 7.63 (1/2H, s), 7.68 (1/2H, s), 7.78 (1H, d, J = 7.4 Hz), 7.86-7.90 (1H, m), 8.39 (1H, d, J = 7.0 Hz), 8.65 (1H, s), 10.73 (1Hx1/2, brs), 10.88 (1Hx1/2, brs).

ESI-MS (m/e): 493 (M+H).

Example 275-(4-acetyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-acetyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.55 (3H, s), 2.98 (3H, brs), 3.09 (3H, brs), 6.70-6.90 (4H, m), 7.23 (1/2H, s), 7.34 (1/2H, s), 7.26 (1/2H, s), 7.33-7.35 (2H, m), 7.38-7.42 (1H, m), 7.65 (1/2H, s), 7.68 (1/2H, s), 7.86-7.91 (3H, m), 8.40 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 3.5 Hz), 10.85 (1/2H, brs), 10.95 (1/2H, brs).

ESI-MS (m/e): 493 (M+H).

Example 285-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-cyano-phenoxy)-1H-benzimidazole

2-hydroxy-benzonitrile and 4-hydroxy-benzonitrile were successively used, and the title compound was obtained as a colourless solid by the same method as in Example 1, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.80 (1H, t, J = 8.8 Hz), 6.86 (1H, d, J = 8.8 Hz), 6.89 (1H, d, J = 8.8 Hz), 7.08 (1H, td, J = 7.6 Hz, 7.4 Hz), 7.34-7.47 (3H, m), 7.47-7.58 (3H, m), 7.67 (1H, d, J = 5.2 Hz), 7.88 (1H, t, J = 7.6 Hz), 8.38 (1H, d, J = 7.6 Hz), 8.65 (1H, d, J = 4.0 Hz), 10.58 (1H, brs)

ESI-MS (m/e): 430 (M+H).

Example 295-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(3-cyano-phenoxy)-1H-benzimidazole

Using 4-fluoro-5-(2-cyano-phenoxy)-2-nitro-phenylamine obtained in Example 28 and 3-hydroxy-benzonitrile, the title compound was obtained as a brown solid by the same process as in Example 28, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.93-6.84 (1H, m), 6.96-7.12 (3H, m), 7.27-7.38 (3H, m), 7.38-7.48 (2H, m), 7.54 (1H, dd, J = 1.6 Hz, 7.6 Hz), 7.68 (1H, d, J = 13.2 Hz), 7.89 (1H, t, J = 7.6 Hz), 8.42 (1H, d, J = 7.6 Hz), 8.65 (1H, s).

ESI-MS (m/e): 430 (M+H).

Example 305-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-(2-hydroxyethyl)-phenoxy)-1H-benzimidazole
monotrifluoroacetic acid salt

Using 4-hydroxyethyl-phenol, the title compound was obtained as a brown solid by the same process as in Example 29, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 2.78 (2H, t, J = 7.0 Hz), 3.72 (2H, t, J = 7.0 Hz), 6.83 (2H, d, J = 8.6 Hz),

6.94 (1H, d, J = 8.6 Hz), 7.19-7.21 (3H, m), 7.41 (1H, s), 7.56 (1H, t, J = 8.6 Hz), 7.63-7.73 (3H, m), 8.11 (1H, t, J = 7.8 Hz), 8.26 (1H, d, J = 7-8 Hz), 8.85 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 449 (M+H).

Example 31

5-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(1-oxy-pyridine-3-yloxy)-1H-benzimidazole

1-oxy-pyridin-3-ol and 4-cyano-phenol were successively used, and, by the same process as in Example 1, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 6.86-6.90 (2H, m), 7.11 (1/2H, ddd, J = 7.3, 2.8, 1.5 Hz), 7.13 (1/2H, ddd, J = 7.3, 2.8, 1.5 Hz), 7.18 (1/2H, dd, J = 7.3, 4.8 Hz), 7.20 (1/2H, dd, J = 7.3, 4.8 Hz), 7.36-7.41 (1H, m), 7.37 (1/2H, s), 7.44 (1/2H, s), 7.48-7.57 (3H, m), 7.60 (1/2H, s), 7.66 (1/2H, s), 8.20 (1/2H, d, J = 2.8 Hz), 8.21 (1/2H, d, J = 2.8 Hz), 8.30 (1/2H, dd, J = 4.8, 1.5 Hz), 8.32 (1/2H, dd, J = 4.8, 1.5 Hz), 8.37 (1H, d, J = 7.0 Hz), 8.65-8.70 (1H, m).

ESI-MS (m/e): 422 (M+H).

Example 32

Production of 2-pyrazine-2-yl-5,6-bis (pyridine-3-yloxy)-1H-benzimidazole

To pyridine 1 ml solution of 4,5-bis-(pyridine-3-yloxy)-benzene-1,2-diamine 15 mg obtained in Example 1 (Step 3) were added pyrazine-2-carboxylic acid 7.7 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 20 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was suspended in phosphorus oxychloride 1 ml, and the reaction liquor was stirred at 100°C overnight. Phosphorus oxychloride was eliminated by distillation under reduced pressure and thereafter, it was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution and thereafter, dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol=15/1+0.1 % ammonia water), and obtained the title compound as yellow solid.

¹H-NMR (CD₃OD) δ : 7.20-7.82 (6H, m), 8.11 (2H, s), 8.20-8.28 (2H, m), 8.67 (1H, s), 8.75 (1H, s), 9.47 (1H, s)

ESI-MS (m/e): 383 (M+H).

Example 33

5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-(4-methanesulphonyl-phenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 9, the title compound was obtained by the same process as in Example 32, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.91 (3H, s), 3.04 (3H, d, J = 1.6 Hz), 6.96 (2H, d, J = 9.0 Hz), 7.14-7.18 (1H, m), 7.19-7.25 (1H, m), 7.35 (1/2H, s), 7.41 (1/2H, s), 7.68 (1/2H, s), 7.73 (1/2H, s), 7.84 (2H, dd, J = 9.0, 1.6 Hz), 8.24 (1H, dd, J = 7.1, 2.7 Hz), 8.32-8.35 (1H, m), 8.59-8.62 (1H, m), 8.69 (1H, d, J = 2.5 Hz), 9.63-9.64 (1H, m), 10.91 (1Hx1/2, brs), 10.8 (1Hx1/2, brs).

ESI-MS (m/e): 460 (M+H).

Example 345-(4-dimethylcarbamoyl-phenoxy)-6-(2-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(4-dimethylcarbamoyl-phenoxy)-5-(2-methanesulphonyl -phenoxy)- benzene-1,2-diamine obtained in Example 20, the title compound was obtained by the same process as in Example 32, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.95 (3/2H, s), 2.99 (3H, brs), 3.05 (3/2H, brs), 3.08 (3H, brs), 6.80-6.91 (3H, m), 6.89-6.95 (3H, s), 7.17-7.24 (1H, m), 7.20 (1/2H, s), 7.35-7.39 (2H, m), 7.35-7.39 (1/2H, m), 7.46-7.54 (1H, m), 7.66 (1/2H, s), 7.70 (1/2H, s), 8.02 (1H, d, J = 7.8 Hz), 8.60 (1H, d, J = 2.4 Hz), 8.67 (1H, dd, J = 2.4, 2.0 Hz), 9.61 (1H, d, J = 2.0 Hz), 10.65 (1/2H, brs), 10.74 (1/2H, brs).

ESI-MS (m/e): 530 (M+H).

Example 355-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 4-(2-cyano-phenoxy)-5-(4-methanesulphonyl-phenoxy)-benzene-1,2-diamine obtained in Example 17, the title compound was obtained as a brown solid by the same process as in Example 32, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CD₃OD) δ : 3.09 (3H, s), 6.91 (1H, d, J = 7.8 Hz), 6.96-7.00 (2H, m), 7.15 (1H, td, J = 7.6Hz, 1.0 Hz), 7.54-7.58 (1H, m), 7.64 (1H, dd, J = 1.6Hz, 7.8 Hz), 7.72 (2H, d, J = 3.5 Hz), 7.87 (2H, d, J = 8.6 Hz), 8.77 (1H, d, J = 2.7 Hz), 8.81-8.85 (1H, dd, J = 1.6Hz, 2.7 Hz), 8.52 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 484 (M+H).

Example 365-(2-methoxy-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-methoxy-phenoxy)-5-(4-methanesulphonyl-phenoxy)-benzene-1,2-diamine obtained in Example 16, the title compound was obtained by the same process as in Example 32, a process

based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.04 (3H, s), 3.71 (3H, d, J = 3.1 Hz), 6.86-6.97 (3H, m), 7.00 (1/2H, s), 7.06-7.14 (3H, m), 7.34 (1/2H, s), 7.36 (1/2H, s), 7.68 (1/2H, s), 7.85 (2H, dd, J = 9.0, 3.1 Hz), 8.56-8.59 (1H, m), 8.65 (1H, dd, J = 4.3, 2.7 Hz), 9.57-9.61 (1H, m), 10.24 (1Hx1/2, brs), 10.34 (1Hx1/2, brs).

ESI-MS (m/e): 489 (M+H).

Example 37

5-(4-dimethylcarbamoyl-phenoxy)-6-(2-methanesulphonyl-phenoxy)-2-thiazol-2-yl-1H-benzimidazole

Using thiazole-2-carboxaldehyde and 4-(4-dimethylcarbamoyl-phenoxy)-5-(2-methanesulphonyl-phenoxy)-benzene-1,2-diamine obtained in Example 20, the title compound was obtained by the same process as in Example 1 (Step 4), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 2.94 (3/2H, s), 2.96 (3H, brs), 3.05 (3/2H, brs), 3.08 (3H, brs), 6.87-6.93 (3H, m), 7.13 (1/2H, brs), 7.16-7.23 (1H, m), 7.34-7.38 (2H, m), 7.45-7.53 (1H, m), 7.51 (1/2H, brs), 7.54-7.56 (1H, m), 7.62 (1/2H, s), 7.66 (1/2H, s), 7.94 (1H, d, J = 3.1 Hz), 8.01 (1H, dd, J = 7.8, 1.6 Hz).

ESI-MS (m/e): 535 (M+H).

Example 38

5-(2-cyano-phenoxy)-2-pyridazine-3-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

To N-methylpyrrolidone 0.3 ml solution of 4-(2-cyano-phenoxy)-5-(4-methanesulphonyl-phenoxy)-benzene-1,2-diamine 15 mg obtained in Example 17 were added successively pyridazine-3-carboxylic acid 3.3 mg, 1-hydroxybenzotriazole 15 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 15 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained residue was dissolved in N-methylpyrrolidone 0.2 ml, and trifluoromethanesulfonic acid triytterbium salt 5 mg was added, and the reaction liquor was stirred at 140°C overnight. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid]. By eliminating the solvent of the obtained fraction under reduced pressure, the title compound was obtained as a brown solid.

¹H-NMR(CD₃OD) δ : 3.10 (3H, s), 6.92 (1H, d, J = 7.6 Hz), 6.99 (2H, d, J = 8.6 Hz), 7.20 (1H, t, J = 7.6 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.64 (1H, d, J = 7.6 Hz), 7.70-7.80 (2H, m), 7.87 (2H, d, J = 8.6 Hz), 7.96-8.02 (1H, m), 8.58 (1H, brs), 9.36 (1H, brs).

ESI-MS (m/e): 484 (M+H).

Example 395-(2-cyano-phenoxy)-2-[1,2,5]-thiadiazol-3-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using [1,2,5]-thiadiazole-3-carboxylic acid, the title compound was obtained as a brown solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.09 (3H, s), 6.90 (1H, d, J = 7.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.19 (1H, t, J = 7.7 Hz), 7.56 (1H, t, J = 7.8 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.72 (1H, s), 7.73 (1H, s), 7.87 (2H, d, J = 8.6 Hz), 9.39 (1H, s).

ESI-MS (m/e): 490 (M+H).

Example 405-(2-cyano-phenoxy)-2-(2H-[1,2,3]-triazol-4-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 2H-[1,2,3]-triazole-4-carboxylic acid, the title compound was obtained as a brown solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.12 (3H, s), 6.91 (1H, d, J = 7.6 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.20 (1H, t, d, J = 7.6 Hz), 7.70 (1H, d, J = 2-7 Hz), 7.87 (2H, d, J = 8.6 Hz), 8.52 (1H, brs).

ESI-MS (m/e): 473 (M+H).

Example 415-(2-cyano-phenoxy)-2-furazane-3-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using furazane-3-carboxylic acid, the title compound was obtained as a brown solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.06 (3H, s), 6.84 (1H, d, J = 7.8 Hz), 6.92 (2H, d, J = 8.6 Hz), 7.15 (1H, t, J = 7.8 Hz), 7.52 (1H, t, J = 7.8 Hz), 7.57-7.62 (2H, m), 7.82 (2H, d, J = 8.6 Hz) ESI-MS (m/e): 474 (M+H).

Example 425-(2-cyano-phenoxy)-2-(4H-[1,2,4]-triazol-3-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using [1,2,4]-triazole-3-carboxylic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.07 (3H, s), 6.92 (1H, d, J = 7.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.19 (1H, t,

J = 7.8 Hz), 7.55 (1H, t, J = 7.8 Hz), 7.63 (1H, d, J = 7.8 Hz), 7.74 (2H, d, J = 6.3 Hz), 7.85 (2H, d, J = 8.6 Hz), 8.73 (1H, s).

ESI-MS (m/e): 473 (M+H).

Example 43

5-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

An 80 % sulphuric acid solution of 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 3.5 mg obtained in Example 5 was stirred at 50°C overnight as the reaction liquor.

The reaction mixture was purified by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and, by eliminating the solvent of the obtained fraction under reduced pressure, the title compound was obtained as a colourless solid.

¹H-NMR (CDCl₃) δ : 5.59 (1H, brs), 6.80 (1H, dd, J = 8.4Hz, 0.8 Hz), 7.01-7.48 (7H, m), 7.88 (1H, td, J = 8.0Hz, 2.0 Hz), 8.16 (1H, dd, J = 8.4Hz, 2.0. Hz), 8.21 (1H, s), 8.27-8.85 (1H, m), 8.38 (1H, d, J = 8.0 Hz), 8.63 (1H, d, J = 8.4 Hz).

ESI-MS (m/e): 424 (M+H).

Example 44

5-(4-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 7, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.82 (2H, d, J = 8.8 Hz), 7.13 (1H, ddd, J = 8.4, 2.6, 1.5 Hz), 7.17 (1H, dd, J = 8.4, 4.8 Hz), 7.13-7.20 (1H, m), 7.30-7.37 (1H, m), 7.38 (1H, ddd, J = 7.7, 40.4, 1.1 Hz), 7.71 (2H, d, J = 8.8 Hz), 7.87 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 8.16 (1H, dd, J = 2.6, 0.7 Hz), 8.25 (1H, dd, J = 4.8, 1.5 Hz), 8.39 (1H, ddd, J = 7.7, 1.1, 0.7 Hz), 8.61 (1H, ddd, J = 4.4, 1.8, 0.7 Hz).

ESI-MS (m/e): 424 (M+H).

Example 45

5-(4-carbamoyl-phenoxy)-6-(pyridine-3-yloxy)-2-thiazol-2-yl-1H-benzimidazole

Using 4-(4,5-diamino-2-(pyridine-3-yloxy)-phenoxy)-benzonitrile obtained in Example 7, the title compound was obtained by the same process as in Example 37 and Example 43, a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.01 (2H, brs), 6.82-6.86 (2H, m), 7.13 (1H, ddd, J = 8.4, 2.9, 1.5 Hz), 7.18 (1H, dd, J = 8.4, 4.6 Hz), 7.29 (1/2H, s), 7.30 (1/2H, s), 7.52-7.54 (1H, m), 7.92 (2H, d, J = 8.8 Hz), 7.61 (1/2H, s), 7.64 (1/2H, s), 7.70-7.75 (2H, m), 7.92 (1H, d, J = 2.9 Hz), 8.21 (1H, d, J

= 2.9 Hz), 8.29 (1H, dd, J = 4.6, 1.5 Hz).

ESI-MS (m/e): 430 (M+H).

Example 46

5-(4-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-cyano-phenoxy)-1H-benzimidazole obtained in Example 28, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 7.86 (2H, d, J = 8.8 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.39 (1H, t, J = 7.6 Hz), 7.45-7.74 (4H, m), 7.78 (2H, d, J = 8.8 Hz), 7.91 (1H, d, J = 7.6 Hz), 7.99 (1H, t, J = 7.6 Hz), 8.30 (1H, d, J = 7.6 Hz), 8.74 (1H, s).

ESI-MS (m/e): 466 (M+H).

Example 47

5-(3-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole monotrifluoroacetic acid salt

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(3-cyano-phenoxy)-1H-benzimidazole obtained in Example 29, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 6.78-6.96 (1H, m), 6.96-7.08 (1H, m), 7.08-7.20 (1H, m), 7.30-7.70 (7H, m), 7.88-8.08 (2H, m), 8.29 (1H, d, J = 7.6 Hz), 8.73 (1H, s).

ESI-MS (m/e): 466 (M+H).

Example 48

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole obtained in Example 17, the title compound was obtained as a straw-coloured solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.12 (3H, s), 6.85 (1H, d, J = 7.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.15 (1H, t, J = 7.8 Hz), 7.42 (1H, t, J = 7.8 Hz), 7.52 (1H, dd, J = 4.3 Hz, 7.0 Hz), 7.64 (2H, brs), 7.83 (2H, d, J = 8.6 Hz), 7.91 (1H, d, J = 7.8 Hz), 8.01 (1H, dd, J = 7.0 Hz, 7.8 Hz), 8.32 (1H, d, J = 7.8 Hz), 8.76 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 501 (M+H).

Example 49

5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(4-methanesulphonyl-phenoxy)-

-1H-benzimidazole obtained in Example 35, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.05 (3H, s), 5.80 (1H, brs), 6.82 (1H, d, J = 7.8 Hz), 6.95-7.00 (3H, m), 7.17 (2H, q, J = 8.2 Hz), 7.36-7.39 (2H, m), 7.76 (1H, d, J = 7.8 Hz), 7.81-7.85 (2H, m), 8.15 (1H, d, J = 7.8 Hz), 8.63 (1H, s), 8.72 (1H, s), 9.66 (1H, s), 10.80 (1H, brs)

ESI-MS (m/e): 502 (M+H).

Example 50

5-(4-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(1-oxy-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(1-oxy-pyridine-3-yloxy)-1H-benzimidazole obtained in Example 31, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.82-6.86 (2H, m), 7.15-7.26 (2H, m), 7.38-7.42 (1H, m), 7.41 (1/2H, s), 7.44 (1/2H, s), 7.54-7.58 (1H, m), 7.62 (1/2H, s), 7.65 (1/2H, s), 7.71-7.75 (2H, m), 8.12-8.16 (1H, m), 8.22-8.27 (1H, m), 8.37 (1H, d, J = 7.0 Hz), 8.64-8.67 (1H, m).

ESI-MS (m/e): 440 (M+H).

Example 51

5-(3-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-(3-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 6, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 7.07 (1H, ddd, J = 0.8, 3.4, 10.3 Hz), 7.36 (1H, dd, J = 1.9, 3.4 Hz), 7.40 (1H, t, J = 10.3 Hz), 7.56 (1H, s), 7.57-7.62 (2H, m), 7.69 (1H, dd, J = 7.2, 10.3 Hz), 7.73 (1H, s), 7.78 (1H, ddd, J = 0.8, 3.8, 11.4 Hz), 8.16 (1H, dt, J = 3.0, 11.0 Hz), 8.29 (1H, dt, J = 0.4, 11.0 Hz), 8.37-8.41 (2H, m), 8.80 (1H, dt, J = 0.4, 3.8 Hz).

ESI-MS (m/e): 424 (M+H)+.

Example 52

5-(2-carbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-hydroxybenzoic acid dimethyl amide and 4-fluoro-5-(2-cyano-phenoxy)-2-nitro phenylamine obtained in Example 28, the title compound was obtained by the same procedures as in Example 1 and Example 43, a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.98 (3H, brs), 3.07 (3H, brs), 5.72 (1H, brs), 6.76-6.83 (3H, m), 6.97 (1/2H, brs), 7.09 (1/2H, dd, J = 7.7, 7.7 Hz), 7.11 (1/2H, dd, J = 7.7, 7.7 Hz), 7.14 (1/2H, s), 7.30-7.35 (3H, m), 7.37-7.40 (1H, m), 7.67 (1H, d, J = 7.7 Hz), 7.86 (1H, ddd, J = 7.7, 7.7, 1.5

Hz), 8.12 (1H, dd, J = 7.7, 1.8 Hz), 8.14 (1H, dd, J = 7.7, 1.8 Hz), 8.38 (1H, d, J = 7.7 Hz), 8.61-8.62 (1H, m), 10.99 (1H, brs).

ESI-MS (m/e): 494 (M+H).

Example 53

5-(2-carbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-thiazol-2-yl-1H-benzimidazole

Using 4-(2-cyano-phenoxy)-5-bis-(4-dimethylcarbamoyl-phenoxy)-benzene-1,2-diamine obtained in Example 52, the title compound was obtained by the same procedures as in Example 37 and Example 43, a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.97 (3H, brs), 3.08 (3H, brs), 5.91 (1/2H, brs), 6.00 (1/2H, brs), 6.75-6.82 (3H, m), 6.93 (1/2H, brs), 7.07-7.13 (1H, m), 7.17 (1H, brs), 7.25 (1/2H, brs), 7.32 (2H, d, J = 8.8 Hz), 7.53 (1H, d, J = 2.9 Hz), 7.65 (2H, d, J = 8.8 Hz), 7.37-7.40 (1H, m), 7.65 (1H, d, J = 7.0 Hz), 7.92-7.93 (1H, m), 8.11 (1/2H, d, J = 6.6 Hz), 8.13 (1/2H, d, J = 6.6 Hz).

ESI-MS (m/e): 500 (M+H).

Example 54

5-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(4-(2-[2,2,2-trifluoro-acetoxy]-ethyl)-phenoxy)-1H-benzimidazole • monotrifluoroacetic acid salt

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-(2-hydroxyethyl)-phenoxy)-1H-benzimidazole obtained in Example 30, and, by the same method as in Example 43, a process based on these or a combination of these with a normal procedure, the reaction mixture was refined by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and the title compound was obtained as a colourless solid by eliminating the solvent of the obtained fraction by distillation under reduced pressure.

¹H-NMR(CD₃OD) δ : 2.94 (2H, t, J = 6.7 Hz), 4.17 (2H, t, J = 6.7 Hz), 6.84 (2H, d, J = 8.6 Hz), 6.90 (1H, d, J = 8.6 Hz), 7.19 (1H, d, J = 8.6 Hz), 7.25 (1H, d, J = 8.6 Hz), 7.41 (1H, s), 7.42-7.48 (1H, m), 7.58 (1H, s), 7.61-7.66 (1H, m), 8.09 (1H, t, J = 7.8 Hz), 8.25 (1H, d, J = 7.8 Hz), 8.83 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 563 (M+H).

Example 55

5-(4-carbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-hydroxy-benzonitrile and 4-fluoro-5-(4-dimethylcarbamoyl-phenoxy)-2-nitro-phenylamine obtained in Example 18, the title compound was obtained by the same procedures as in Example 1 and Example 43, a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.97 (3H, brs), 3.08 (3H, brs), 6.80-6.86 (4H, m), 7.26-7.29 (2H, m), 7.31 (1/2H, s), 7.35 (1/2H, s), 7.38-7.41 (1H, m), 7.66-7.70 (3H, m), 7.86-7.91 (1H, m), 8.40 (1H, d, J

= 7.8 Hz), 8.65 (1H, d, J = 4.7 Hz), 10.89 (1H, brs).

ESI-MS (m/e): 494 (M+H).

Example 56

5-(4-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

To methanol 1 ml solution of 5-(4-methoxycarbonyl-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 3.0 mg obtained in Example 10 was added 40 % methylamine methanol solution 0.05 ml, and the reaction liquor was stirred at room temperature overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol=20/1), and the title compound was obtained.

¹H-NMR (CDCl₃) δ : 2.96 (3/2H, s), 2.97 (3/2H, s), 6.80 (1H, d, J = 8.4 Hz), 7.14-7.23 (2H, m), 7.36 (1H, brs), 7.40 (1H, dd, J = 7.7, 4.7 Hz), 7.62 (1H, brs), 7.66 (2H, d, J = 8.4 Hz), 7.90 (1H, dd, J = 7.7, 7.7 Hz), 8.10 (1H, brs), 8.20 (1H, brs), 8.37 (1H, d, J = 7.7 Hz), 8.63 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 438 (M+H).

Example 57

5-(4-methanesulphonyl-phenoxy)-6-(2-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-(2-ethoxycarbonyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole obtained in Example 14, the title compound was obtained by the same process as in Example 56, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.73 (3/2H, s), 2.74 (3/2H, s), 3.03 (3H, s), 6.74-6.79 (1H, m), 6.89-7.06 (2H, m), 7.01 (1/2H, brs), 7.09-7.15 (1H, m), 7.17 (1/2H, brs), 7.30 (1/2H, brs), 7.40 (1/2H, brs), 7.40-7.44 (1H, m), 7.72 (1H, s), 7.82 (2H, dd, J = 8.2, 6.7 Hz), 7.88-7.93 (1H, m), 8.10-8.15 (1H, m), 8.41 (1H, d, J = 6.8 Hz), 8.66 (1H, ts), 11.09 (1/2H, brs), 11.12 (1/2H, brs).

ESI-MS (m/e): 515 (M+H).

Example 58

5-(4-dimethylcarbamoyl-phenoxy)-6-(2-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-(2-ethoxycarbonyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole obtained in Example 24, the title compound was obtained by the same process as in Example 56, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.77 (3H, d, J = 3.5 Hz), 2.99 (3H, brs), 3.08 (3H, brs), 6.75-6.86 (3H, m), 7.00-7.14 (1H, m), 7.15-7.27 (1/2H, m), 7.27-7.32 (2H, m), 7.27-7.32 (1/2H, m), 7.35-7.42 (2H,

m), 7.69 (1H, s), 7.87-7.91 (1H, m), 8.11-8.17 (1H, m), 8.40 (1H, d, J = 7.4 Hz), 8.66 (1H, s), 11.01 (1H, brs).

ESI-MS (m/e): 508 (M+H).

Example 59

5-(2-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-(2-fluoro-4-nitro-phenoxy)-pyridine obtained in Example 1 (Step 2) and 2-hydroxybenzoic acid ethyl ester, the title compound was obtained as a brown solid by the same procedures as in Example 1 and Example 56, a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.70-8.80 (3H, m), 6.77 (1H, d, J = 7.6 Hz), 7.25-7.44 (7H, m), 7.67 (1H, s), 7.82 (1H, t, J = 7.6 Hz), 8.15 (1H, t, J = 7.6 Hz), 8.18-8.26 (1H, m), 8.26-8.36 (1H, m), 8.38 (1H, d, J = 7.6 Hz), 8.64 (1H, d, J = 2.4 Hz), 10.6 (1H, brs).

ESI-MS (m/e): 438 (M+H).

Example 60

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-(2H-tetrazol-5-yl)-phenoxy)-1H-benzimidazole • monotrifluoroacetic acid salt

To dimethylformamide 1 ml solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-cyano-phenoxy)-1H-benzimidazole 30 mg obtained in Example 17, sodium azide 30 mg and magnesium chloride 32 mg were added, and the reaction liquor was stirred at 170°C for 24 hours. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as yellow solid.

¹H-NMR(CD₃OD) δ : 3.11 (3H, s), 6.75 (2H, d, J = 8.6 Hz), 6.96 (1H, d, J = 7.6 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.51 (1H, t, J = 7.6 Hz), 7.62 (2H, d, J = 8.6 Hz), 7.58-7.69 (1H, m), 7.73 (1H, s), 7.93 (1H, s), 8.13 (1H, d, J = 7.6 Hz), 8.08-8.16 (1H, m), 8.33-8.38 (1H, m), 8.84-8.88 (1H, m).

ESI-MS (m/e): 526 (M+H).

Example 61

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-(2-(N-hydroxycarbamimidoyl)-phenoxy)-1H-benzimidazole

To ethanol 2 ml solution of 5-(4-methanesulphonyl -phenoxy)-2-pyridine-2-yl-6-(2-cyano-phenoxy)-1H-benzimidazole 25 mg obtained in Example 17, 50 % hydroxylamine aqueous solution 0.1 ml was added, and the reaction liquor was stirred at 50°C overnight. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744

(Merck Co.), chloroform/methanol=5/1), and obtained the title compound as a colourless solid.

¹H-NMR (CDCl₃) δ : 3.06 (3H, s), 5.12 (2H, s), 6.52 (1H, s), 6.80 (1H, d, J = 7.6 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.28 (1H, t, J = 7.6 Hz), 7.47 (1H, dd, J = 7.8 Hz, 4.3 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.66 (1H, s), 7.89 (2H, d, J = 8.6 Hz), 7.96 (1H, t, J = 7.8 Hz), 8.55 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 516 (M+H).

Example 62

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-(2-oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)-phenoxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.25 ml solution of 5-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole 8 mg obtained in Example 61 was added 1,1'-carbonyldiimidazole 10 mg, and the reaction liquor was stirred at 70°C for four hours. The reaction mixture was refined by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and the obtained fraction was diluted with ethyl acetate, and was washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, and thereafter, was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a colourless solid.

¹H-NMR (CDCl₃) δ : 3.12 (3H, s), 6.84 (2H, d, J = 8.6 Hz), 6.82-6.88 (1H, m), 7.19 (1H, t, J = 7.2 Hz), 7.41-7.47 (2H, m), 7.82 (2H, d, J = 8.6 Hz), 7.91-7.97 (2H, m), 8.44 (1H, d, J = 7.8 Hz), 8.69 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 542 (M+H).

Example 63

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-[1,2,4]-oxadiazol-3-yl-phenoxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.25 ml solution of 5-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole 8 mg obtained in Example 61 was added ortho ethyl formate ester 0.5 ml, and the reaction liquor was stirred at 100°C for three hours. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and thereafter, it was purified by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol=10/1), and the obtained the title compound as yellow solid.

¹H-NMR (CDCl₃) δ : 3.03 (3H, s), 6.85-6.97 (3H, m), 7.23 (1H, t, J = 7.8 Hz), 7.40-7.45 (3H, m), 7.68-7.74 (3H, m), 7.91 (1H, t, J = 7.8 Hz), 8.03 (1H, d, J = 7.8 Hz), 8.42 (1H, d, J = 7.8 Hz),

8.65-8.68 (2H, m).

ESI-MS (m/e): 526 (M+H).

Example 64

5-(pyridine-3-yloxy)-2-pyridine-2-yl-6-(2-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 5, the reaction liquor added acetic anhydride 0.3 ml to pyridine 0.5 ml solution of 5-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 20 mg obtained by same process as in Example 61 was stirred at 60°C overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol=10/1), and obtained the title compound as straw-coloured solid.

¹H-NMR (CDCl₃) δ : 6.80-7.00 (1H, m), 7.00-7.30 (4H, m), 7.30-7.44 (2H, m), 7.44-7.68 (1H, m), 7.86 (1H, td, J = 7.6Hz, 2.0 Hz), 7.97 (1H, dd, J = 2.0Hz, 7.6 Hz), 8.38 (1H, d, J = 7.6 Hz), 8.60 (1H, d, J = 4.8 Hz).

ESI-MS (m/e): 463 (M+H).

Example 65

5-(4-methyl-pyridine-3-sulfonyl)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

To tetrahydrofuran 1.5 ml solution of 5-(2-methyl-pyridin-5-yl sulphanyl)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 42 mg obtained in Example 13 were added OXONE 92 mg and water 0.1 ml, and the reaction liquor was stirred at room temperature overnight. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid]. Saturated aqueous sodium bicarbonate was added to the obtained fraction and thereafter, it was extracted with chloroform and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

¹H-NMR (CDCl₃) δ : 2.63 (3H, s), 7.23 (1H, s), 7.32 (1H, d, J = 7.6 Hz), 7.44-7.50 (3H, m), 7.93 (1H, t, J = 7.6 Hz), 8.09-8.14 (1H, m), 8.28 (1H, d, J = 2.8 Hz), 8.36-8.41 (2H, m), 8.60, 8.61 (tautomer, 1H, s), 8.68 (1H, d, J = 4.8 Hz), 8.93, 8.95 (tautomer, 1H, d, J = 2.0 Hz).

ESI-MS (m/e): 444 (M+H).

Example 66

5-(4-methanesulphonyl-phenoxy)-2-(1-oxy-pyridine-2-yl)-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

To chloroform 2 ml solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole 8.0 mg obtained in Example 48 was added metachloroperbenzoic acid 1.5 mg, and the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid]. By eliminating the solvent of the obtained fraction under reduced pressure, the title compound was obtained as yellow solid.

¹H-NMR(CD₃OD) δ : 3.12 (3H, s), 6.87 (1H, d, J = 7.8 Hz), 7.00 (2H, d, J = 7.8 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.43 (1H, t, J = 7.8 Hz), 7.69-7.76 (2H, m), 7.84-7.86 (3H, m), 7.92 (1H, d, J = 7.8 Hz), 8.52 (1H, d, J = 7.0 Hz), 8.64 (1H, d, J = 7.8 Hz).

ESI-MS (m/e): 517 (M+H).

Example 67

4-(2-methoxy-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Step 1

Synthesis of 5-fluoro-3-(2-methoxyphenoxy)-2-nitroaniline

To 2-methoxyphenol 1.64 g dissolved in tetrahydrofuran 30 ml was added sodium hydride 528 mg under ice cooling, and the reaction liquor was stirred for 30 minutes at the same temperature. Successively, 1.91 g of 3,5-difluoro-2-nitroaniline synthesised using process described in Journal of Organic Chemistry, 1978, Vol. 43, issue 6, pp.1241-1243 was added, and the reaction liquor was stirred at room temperature for two days. The reaction liquor was poured into water and was dried with anhydrous magnesium sulphate after extraction with ethyl acetate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1-4/1), and the title compound was obtained as orange colored solid.

Step 2

Synthesis of 3-(2-methoxyphenoxy)-2-nitro-5-(pyridine-3-yloxy)-aniline

To 5-fluoro-3-(2-methoxyphenoxy)-2-nitroaniline 3.03 g dissolved in dimethylformamide 30 ml were added 3-hydroxypyridine 1.24 g and potassium carbonate 5.42 g, and the reaction liquor was stirred at 90°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1-1/1-1/2), and the title compound was obtained as orange colored solid.

Step 3Synthesis of 3-(2-methoxyphenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine

To methanol 20 ml solution of 3-(2-methoxyphenoxy)-2-nitro-5-(pyridine-3-yloxy)-aniline 1.33 g was added 20 % palladium hydroxide-carbon catalyst 1 g, and the reaction liquor was stirred under a hydrogen atmosphere for four hours. After eliminating the catalyst by filtration, the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2-ethyl acetate), and the title compound was obtained as pale orange color oily substance.

Step 4Production of 4-(2-methoxy-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Pyridine-2-carboxaldehyde 0.026 ml was added to nitrobenzene 0.5 ml solution of 3-(2-methoxyphenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine 59 mg at 120°C, and the reaction liquor was stirred at the same temperature for one hour. The reaction mixture was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-acetic acid to chloroform/methanol = 20/1). Solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol=20/1), and obtained the title compound as straw-coloured solid.

¹H-NMR (CDCl₃) δ : 3.79 and 3.83 (total 3H, each s), 6.20-7.40 (9H, m), 7.80-7.88 (1H, m), 8.24-8.65 (4H, m), 10.68-10.94 (1H, m).

ESI-MS (m/e): 411 (M+H).

Example 684-(4-fluoro-phenoxy)-2-pyrazine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-fluorophenol and 3-hydroxypyridine, pyrazine-2-carboxylic acid 18.6 mg and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 57.5 mg were added to pyridine 2 ml solution of 3-(4-fluorophenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine 46.7 mg synthesised by the same process as in Example 67, and the reaction liquor was stirred overnight, and thereafter, pyridine was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, was dried with anhydrous magnesium sulphate. By eliminating the solvent under reduced pressure, mixture of amide body was obtained as a yellow oily substance. The obtained mixture of amide body was dissolved in toluene 3 ml, and p-toluenesulfonic acid monohydrate 28 mg was added, and the reaction liquor was stirred at 120°C overnight. The reaction liquor was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄,

Art5744 (Merck Co.), chloroform/methanol=20/1), and obtained the title compound as yellow solid.

¹H-NMR (CDCl₃) δ : 6.35 and 6.53 (total 1H, each d, J = 2.0 Hz), 6.77-7.31 (7H, m), 8.32-8.40 (2H, m), 8.54 and 8.56 (total 1H, each d, J = 1.8 Hz), 8.61 and 8.64 (total 1H, each d, J = 2.6 Hz), 9.59 and 9.69 (total 1H, each d, J = 1.5 Hz), 10.60 (1H, brs).

ESI-MS (m/e): 400 (M+H).

Example 69

6-(4-methoxy-phenoxy)-4-(1-methyl-1H-imidazol-2-yl sulphanyl)-2-pyridine-2-yl-1H-benzimidazole

Using 1-methyl-1H-imidazole-2-thiol and 4-methoxyphenol successively, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

¹H-NMR (CDCl₃) δ : 3.73 and 3.74 (total 3H, each s), 3.81 (3H, s), 6.31-7.39 (9H, m), 7.78-7.88 (1H, m), 8.30 and 8.41 (total 1H, each d, J = 7.8 Hz), 8.59 and 8.73 (total 1H, each d, J = 4.5 Hz).

ESI-MS (m/e): 430 (M+H).

Example 70

6-(4-methoxy-phenoxy)-2-pyridine-2-yl-4-(pyridin-2-yl sulphanyl)-1H-benzimidazole

Pyridine-2-thiol and 4-methoxyphenol were successively used, and the title compound was obtained as a straw-coloured solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.80 and 3.81 (total 3H, each s), 6.86-7.50 (10H, m), 7.75-7.88 (1H, m), 8.32-8.62 (3H, m).

ESI-MS (m/e): 427 (M+H).

Example 71

6-(3-methoxy-phenoxy)-4-(2-methoxy-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2-methoxyphenoxy)-2-nitro-5-(pyridine-3-yloxy)-aniline obtained in Example 67 (Step 2) and 3-methoxyphenol, the title compound was obtained as a white solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.75 (3H, s), 3.79 and 3.84 (total 3H, each s), 6.24-7.23 (10H, m), 7.29-7.39 (1H, m), 7.79-7.89 (1H, m), 8.37 and 8.53 (total 1H, each d, J = 7.5 Hz), 8.56-8.65 (1H, m), 10.53-10.83 (1H, m).

ESI-MS (m/e): 440 (M+H).

Example 72

4-(2-methoxy-phenoxy)-6-(pyridine-3-yloxy)-2-thiazol-2-yl-1H-benzimidazole

Using 3-(2-methoxyphenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 67 (Step 3) and 2-thiazole carboxaldehyde, the title compound was obtained as yellow solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.78 and 3.82 (total 3H, each s), 6.20 and 6.44 (total 1H, each s), 6.68-7.28 (7H, m), 7.43-7.53 (1H, m), 7.88-7.98 (1H, m), 8.29-8.41 (2H, m), 10.90-11.10 (1H, m).

ESI-MS (m/e): 417 (M+H).

Example 73

4-(2-fluoro-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-fluorophenol, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.18-6.78 (2H, m), 6.98-7.42 (8H, m), 7.72-7.90 (1H, m), 8.22-8.66 (3H, m), 11.3 (1H, brs).

ESI-MS (m/e): 399 (M+H).

Example 74

4-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-fluorophenol, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.39 (1H, d, J = 2.1 Hz), 6.84 (1H, d, J = 2.1 Hz) 7.17-7.25 (4H, m), 7.39 (1H, dd, J = 8.4, 4.7 Hz), 7.45 (1H, ddd, J = 8.4, 2.8, 1.5 Hz), 7.50 (1H, dd, J = 7.7, 4.9 Hz), 7.96 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 8.22 (1H, d, J = 7.7 Hz), 8.33 (1H, dd, J = 4.7, 1.5 Hz), 8.38 (1H, d, J = 2.8 Hz), 8.69 (1H, ddd, J = 4.9, 1.8, 1.1 Hz).

ESI-MS (m/e): 399 (M+H).

Example 75

4-(3-fluoro-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-fluorophenol, the title compound was obtained as pale-brown solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.47-6.98 (5H, m), 7.19-7.39 (4H, m), 7.78-7.89 (1H, m), 8.29-8.48 (3H, m), 8.58 (1H, s).

ESI-MS (m/e): 399 (M+H).

Example 76

2-pyridine-2-yl-4,6-bis (pyridine-3-yloxy)-1H-benzimidazole

Using 3-hydroxypyridine, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 7.07 (1H, d, J = 2.0 Hz), 7.30 (1H, d, J = 2.0 Hz), 7.54 (1H, ddd, J = 7.6Hz, 4.8 Hz, 1.2 Hz), 7.85-7.95 (2H, m), 7.98 (1H, td, J = 7.6Hz, 2.0 Hz), 8.10-8.40 (2H, m), 8.22 (1H, d, J = 8.8 Hz), 8.48-8.60 (2H, m), 8.66 (1H, d, J = 2 Hz), 8.70-8.82 (2H, m)

ESI-MS (m/e): 382 (M+H).

Example 77

4-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-2-yloxy)-1H-benzimidazole

2-cyanophenol and 2-hydroxypyridine were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 6.60-7.40 (3H, m), 6.92 (1H, d, J = 8.0 Hz), 6.99 (1H, dd, J = 6.4Hz, 5.2 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.46 (1H, dd, J = 8.0Hz, 2.4 Hz), 7.58-7.70 (2H, m), 7.70-7.90 (1H, m), 8.18 (1H, dd, J = 4.8Hz, 1.2 Hz), 8.38 (1H, d, J = 8.0 Hz), 8.60 (1H, d, J = 4.0 Hz), 10.40-11.00 (1H, m).

ESI-MS (m/e): 406 (M+H).

Example 78

4-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-cyanophenol, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 6.55 (1/2H, s), 6.69 (1/2H, s), 6.70-7.55 (8H, m), 7.58-7.72 (1H, m), 7.76-7.80 (1H, m), 8.26-8.48 (3H, m), 8.55-8.64 (1H, m), 10.8-11.4 (1H, m).

ESI-MS (m/e): 406 (M+H).

Example 79

4-(2-methoxycarbonyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole ditrifluoroacetic acid salt

Using 2-hydroxybenzoic acid methyl ester, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.70 (3H, s), 6.38 (1H, s), 7.14 (1H, s), 7.34 (1H, d, J = 7.6 Hz), 7.39 (1H, t, J = 7.6 Hz), 7.50-7.75 (3H, m), 7.75-7.88 (1H, m), 7.99 (1H, dd, J = 7.6Hz, 1.2 Hz), 8.07 (1H, t, J = 7.6 Hz), 8.27-8.58 (3H, m), 8.72-8.88 (1H, m).

ESI-MS (m/e): 439 (M+H).

Example 80

4-(2-acetyl-phenoxy)-2-(pyridine-2-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-hydroxyacetophenone, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.68 (3H, s), 6.58 (1H, d, J = 2.3 Hz), 7.19 (1H, dd, J = 1.2, 8.2 Hz), 7.31 (1H, dd, J = 1.2, 7.5 Hz), 7.35 (1H, dd, J = 1.0, 7.5 Hz), 7.53-7.62 (2H, m), 7.69 (1H, dd, J = 4.7, 7.8 Hz), 7.76-7.82 (1H, m), 7.87 (1H, dd, J = 1.0, 8.2 Hz), 8.10 (1H, t, J = 7.8 Hz), 8.50-8.52 (1H, m), 8.54 (1H, d, J = 2.3 Hz), 8.62 (1H, d, J = 7.0 Hz), 8.74 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 423 (M+H).

Example 81

4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-hydroxy-1-methyl-1H-pyridin-2-one, the title compound was obtained as a straw-coloured solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.62 (3H, s), 6.02-7.40 (8H, m), 7.84 (1H, t, J = 7.2 Hz), 8.33 (1H, d, J = 4-4 Hz), 8.33-8.50 (2H, m), 8.52-8.70 (1H, m)

ESI-MS (m/e): 412 (M+H).

Example 82

6-(4-dimethylcarbamoyl-phenoxy)-4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

¹H-NMR (CDCl₃) δ : 3.03 and 3.09 (total 6H, each s), 3.60 and 3.64 (total 3H, each s), 6.08-6.15 (1H, m), 6.42 and 6.64 (total 1H, each s), 6.82-7.41 (8H, m), 7.80-7.88 (1H, m), 8.36 and 8.45 (total 1H, each d, J = 8.2 Hz), 8.59 and 8.64 (total 1H, each d, J = 4.5 Hz).

ESI-MS (m/e): 482 (M+H).

Example 83

4-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

2-difluoromethoxy-3-hydroxypyridine and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a straw-coloured solid.

¹H-NMR (CDCl₃) δ : 3.02 and 3.09 (total 6H, each s), 6.36 and 6.48 (total 1H, each s), 6.84-7.67 (9H, m), 7.83 and 7.88 (total 1H, each t, J = 7.8 Hz), 7.99 and 8.00 (total 1H, each d, J = 5.0 Hz), 8.40 and 8.42 (total 1H, each d, J = 8.4 Hz), 8.61 and 8.64 (total 1H, each d, J = 4.3 Hz).

ESI-MS (m/e): 518 (M+H).

Example 846-(2-methyl-pyridin-5-yl sulphanyl)-2-(pyridine-2-yl)-4-(pyridine-3-yloxy)-1H-benzimidazole

3-hydroxypyridine and 6-methylpyridine-3-thiol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 2.52 (3H, s), 6.66-6.80 (1H, brs), 7.05 (1H, d, J = 8.0 Hz), 7.20-7.28 (3H, m), 7.32 (1H, m), 7.49 (1H, dd, J = 2.0Hz, 8.0 Hz), 7.81 (1H, t, J = 7.6 Hz), 8.32-8.40 (3H, m), 8.44 (1H, d, J = 2.0 Hz), 8.52 (1H, d, J = 4.8 Hz), 11.70-12.0 (1H, brs)

ESI-MS (m/e): 412 (M+H).

Example 854-(2-cyano-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H- benzimidazole

2-cyanophenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CDCl₃) δ : 3.05 (3H, s), 3.18 (3H, s), 6.62 (1H, s), 6.92-7.08 (3H, m), 7.00 (2H, d, J = 8.8 Hz), 7.10-7.20 (2H, m), 7.36-7.50 (4H, m), 7.40 (2H, d, J = 8.8 Hz), 7.63 (1H, d, J = 6.3 Hz), 7.89 (1H, t, J = 7.8 Hz), 8.44 (1H, d, J = 7.8 Hz), 8.61 (1H, d, J = 3.9 Hz).

ESI-MS (m/e): 476 (M+H).

Example 864-(2-fluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H- benzimidazole

Using 2-fluorophenol and 4-hydroxy-N,N-dimethylbenzamide successively, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.02 (3H, s), 3.10 (3H, s), 6.39 (1H, s), 6.92-7.00 (3H, m), 6.96 (2H, d, J = 9.0 Hz), 7.10-7.24 (4H, m), 7.36-7.42 (3H, m), 7.39 (2H, d, J = 9.0 Hz), 7.88 (1H, d, J = 7.7 Hz), 8.51 (1H, d, J = 8.0 Hz), 8.63 (1H, d, J = 7.7 Hz).

ESI-MS (m/e): 469 (M+H).

Example 874-(2-fluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H- benzimidazole

2-fluorophenol and 4-(methanesulphonyl)-phenol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 3.08 (3H, s), 6.44 (1H, s), 7.08 (2H, d, J = 9.0 Hz), 7.18-7.57 (5H, m), 7.59 (1H, dd, J = 3.1, 8.2 Hz), 7.90 (2H, d, J = 9.0 Hz), 8.06 (1H, t, J = 7.6 Hz), 8.64 (1H, d, J = 8.2 Hz), 18.71 (1H, d, J = 7.6 Hz).

ESI-MS (m/e): 476 (M+H).

Example 88**4-(2-(1-hydroxy-ethyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole**

2-(1-hydroxyethyl)-phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 1.48 (3H, d, J = 6.4 Hz), 3.05 (3H, s), 3.10 (3H, s), 5.26 (1H, q, J = 6.4 Hz), 6.34 (1H, s), 7.04 (2H, d, J = 9.0 Hz), 7.05-7.10 (2H, m), 7.29-7.33 (2H, m), 7.44 (2H, d, J = 9.0 Hz), 7.57 (1H, dd, J = 4.7, 7.6 Hz), 7.68 (1H, dd, J = 2.0, 7.4 Hz), 8.04 (1H, dt, J = 1.6, 7.8 Hz), 8.37 (1H, d, J = 7.8 Hz), 8.80 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 495 (M+H).

Example 89**4-(2-methanesulphonyl-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole**

2-(methanesulphonyl)-phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 3.06 (3H, s), 3.14 (3H, s), 3.49 (3H, s), 7.03 (1H, d, J = 2.0 Hz), 7.11 (2H, d, J = 8.8 Hz), 7.22 (1H, d, J = 8.0 Hz), 7.32-7.40 (2H, m), 7.42 (1H, d, J = 2.0 Hz), 7.48 (2H, d, J = 9.0 Hz), 7.57 (1H, dd, J = 4.9, 7.8 Hz), 7.63 (1H, dd, J = 1.8, 7.9 Hz), 8.00 (1H, dt, J = 1.6, 7.8 Hz), 8.14 (1H, dd, J = 1.8, 8.0 Hz), 8.52 (1H, d, J = 8.0 Hz), 8.75 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 529 (M+H).

Example 90**4-(2-acetyl-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole**

2-hydroxy-acetophenone and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 2.68 (3H, s), 3.10 (3H, s), 3.20 (3H, s), 6.67 (1H, s), 7.05 (2H, d, J = 8.2 Hz), 7.15-7.22 (2H, m), 7.35 (1H, t, J = 7.0 Hz), 7.45 (2H, d, J = 8.2 Hz), 7.55 (1H, t, J = 7.0 Hz), 7.60-7.64 (1H, m), 7.86 (1H, d, J = 7.4 Hz), 8.08-8.14 (1H, m), 8.64 (1H, d, J = 7.4 Hz), 8.75-8.77 (1H, m)

ESI-MS (m/e): 493 (M+H).

Example 91

4-(2-dimethylcarbamoyl-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2-hydroxy-N,N-dimethylbenzamide and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 2.99 (3H, s), 3.06 (6H, s), 3.17 (3H, s), 6.91-6.94 (1H, m), 7.04 (2H, d, J = 8.6 Hz), 7.06-7.10 (1H, m), 7.17 (1H, t, J = 7.4 Hz), 7.28-7.39 (4H, m), 7.42 (2H, d, J = 8.6 Hz), 7.84 (1H, t, J = 7.8 Hz), 8.41 (1H, d, J = 7.8 Hz), 8.68 (1H, .d, J = 3.9 Hz).

ESI-MS (m/e): 522 (M+H).

Example 92

4-(2,5-difluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2,5-difluoro phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 3.02 (3H, s), 3.14 (3H, s), 6.52-6.55 (1H, m), 6.90-6.99 (2H, m), 7.02 (2H, d, J = 8.2 Hz), 7.10 (1H, d, J = 2.0 Hz), 7.16-7.24 (1H, m), 7.42 (2H, d, J = 8.2 Hz), 7.54-7.60 (1H, m), 8.06 (1H, dt, J = 1.6, 7.8 Hz), 8.61 (1H, d, J = 7.8 Hz), 8.72 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 487 (M+H).

Example 93

4-(2,4-difluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2,4-difluoro phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 3.00 (3H, s), 3.09 (3H, s), 6.31 (1H, s), 6.99 (1H, s), 7.02 (2H, d, J = 8.6 Hz), 7.10-7.25 (2H, m), 7.28-7.40 (1H, m), 7.43 (2H, d, J = 8.6 Hz), 7.49-7.52 (1H, m), 7.98 (1H, d, J = 7.8 Hz), 8.34 (1H, d, J = 7.9 Hz), 8.74 (1H, d, J = 3.9 Hz).

ESI-MS (m/e): 487 (M+H).

Example 94

4-(2,6-difluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2,6-difluoro phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 3.02 (3H, s), 3.14 (3H, s), 6.39 (1H, s), 7.00 (2H, d, J = 8.6 Hz), 7.06-7.18 (3H, m), 7.20-7.25 (1H, m), 7.41 (2H, d, J = 8.6 Hz), 7.48-7.51 (1H, m), 7.99 (1H, dt, J = 1.6, 7.8 Hz), 8.59 (1H, d, J = 8.2 Hz), 8.70 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 487 (M+H).

Example 95

4-(2-methoxy-phenoxy)-2-(pyridine-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 4-(methanesulphonyl) phenol, the title compound was obtained by the same process as in Example 71, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.03 (3H, s), 3.79 (3H, s), 6.32 (1H, s), 6.92-6.99 (1H, m), 7.00 (1H, s), 7.06 (2H, d, J = 8.6 Hz), 7.10-7.22 (3H, m), 7.38-7.43 (1H, m), 7.83 (2H, d, J = 8.6 Hz), 7.90 (1H, t, J = 7.8 Hz), 8.50 (1H, d, J = 7.8 Hz), 8.64 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 488 (M+H).

Example 96

6-(4-dimethylcarbamoyl-phenoxy)-4-(1-ethyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

1-ethyl-3-hydroxy-1H-pyridin-2-one and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a straw-coloured solid.

¹H-NMR (CDCl₃) δ : 1.38 (3H, t, J = 6.8 Hz), 3.02 and 3.09 (total 6H, each s), 4.06 (2H, q, J = 6.8 Hz), 6.15 (1H, t, J = 7.0 Hz), 6.40-7.42 (9H, m), 7.78-7.86 (1H, m), 8.32-8.42 (1H, m), 8.57-8.66 (1H, m).

ESI-MS (m/e): 496 (M+H).

Example 97

6-(6-methyl-pyridine-3-yl phenyl)-4-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-2-(pyridine-2-yl)-1H-benzimidazole

4-methyl-4H-[1,2,4] triazole-3-thiol and 6-methyl-pyridine-3-thiol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 2.55 (3H, s), 3.71 (3H, s), 7.17 (1H, d, J = 8.0 Hz), 7.20-7.24 (1H, brs), 7.42-7.46 (1H, m), 7.59 (1H, dd, J = 2.4 Hz, 8.0 Hz), 7.66-7.68 (1H, brs), 7.91 (1H, t, J = 8.0 Hz), 8.32-8.38 (3H, m), 8.70 (1H, d, J = 4.8 Hz).

ESI-MS (m/e): 432 (M+H).

Example 98

4-(4-fluoro-phenoxy)-2-(5-methyl-isoxazol-3-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-methylisoxazole-3-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 2.50 (3H, s), 6.40 (1H, s), 6.80 (1H, s), 6.82 (1H, brs), 7.14-7.24 (4H, m), 7.38 (1H, dd, J = 8.2, 4.7 Hz), 7.44 (1H, d, J = 7.7 Hz), 8.32 (1H, d, J = 4.7 Hz), 8.36 (1H, d, J = 2.5 Hz).

ESI-MS (m/e): 403 (M+H).

Example 99

4-(4-fluoro-phenoxy)-2-(1-methyl-1H-imidazol-4-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-imidazole-4-carboxylic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 3.72 (3H, s), 6.38 (1H, d, J = 1.8 Hz), 6.81 (1H, d, J = 1.8 Hz), 7.05-7.13 (2H, m), 7.17 (2H, t, J = 8.8 Hz), 7.36-7.43 (2H, m), 7.75 (1H, s), 7.78 (1H, d, J = 1.1 Hz), 8.28 (1H, s), 8.35 (1H, d, J = 2.2 Hz).

ESI-MS (m/e): 402 (M+H).

Example 100

4-(4-fluoro-phenoxy)-2-(3-methyl-[1,2,4]thiadiazol-5-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole • monotrifluoroacetic acid salt

Using 3-methyl [1,2,4] thiadiazole-5-carboxylic acid synthesised by a process in accordance with patent EP0726260 and by combining this process with normal method, the title compound was obtained as a brown solid by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 2.70 (3H, s), 6.44 (1H, d, J = 2.2 Hz), 6.87 (1H, s), 7.15-7.27 (4H, m), 8.39 (1H, dd, J = 4.5, 1.5 Hz), 8.44 (1H, d, J = 2.5 Hz).

ESI-MS (m/e): 420 (M+H).

Example 101

4-(4-fluoro-phenoxy)-2-isoxazol-3-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using isoxazole-3-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 6.41 (1H, d, J = 2.4 Hz), 7.01 (1H, d, J = 2.4 Hz), 7.02-7.20 (5H, m), 7.51 (1H, dd, J = 4.4 Hz, 8.4 Hz), 7.59 (1H, dd, J = 2.4 Hz, 8.4 Hz), 8.32 (1H, d, J = 4.4 Hz), 8.35 (1H, d, J = 2.4 Hz), 8.84 (1H, d, J = 2.4 Hz).

ESI-MS (m/e): 389 (M+H).

Example 1024-(4-fluoro-phenoxy)-2-pyrimidine-4-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using pyrimidine-4-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.60 (3H, s), 6.98-7.40 (8H, m), 8.30-8.50 (2H, m), 8.63 (1H, s), 10.40-11.00 (1H, m).

ESI-MS (m/e): 400 (M+H).

Example 1034-(4-fluoro-phenoxy)-2-pyrimidine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using pyrimidine-2-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CD₃OD) δ : 6.42 (1H, s), 6.98 (1H, s), 7.10-7.30 (5H, m), 7.36-7.60 (2H, m), 8.22-8.42 (2H, m), 8.90-9.10 (1H, m), 9.20 (1H, s).

ESI-MS (m/e): 400 (M+H).

Example 1044-(4-fluoro-phenoxy)-2-(1H-imidazol-2-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 1H-imidazole-2-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 6.44 (1H, d, J= 2.0 Hz), 7.00 (1H, d, J = 2.0 Hz), 7.05-7.18 (4H, m), 7.25 (2H, s), 7.39 (1H, dd, J = 3,2Hz, 8.4 Hz), 7.42-7.50 (1H, m), 8.26 (1H, dd, J = 1.6Hz, 4.4 Hz), 8.29 (1H, d, J = 3.2 Hz).

ESI-MS (m/e): 388 (M+H).

Example 1054-(4-fluoro-phenoxy)-2-(1-methyl-1H-imidazol-2-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-imidazole-2-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.98-4.38 (3H, m), 6.38-6.60 (1H, m), 6.60-6.80 (1H, m), 6.80-7.40 (8H, m), 8.20-8.44 (2H, m)

ESI-MS (m/e): 402 (M+H).

Example 1064-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-2-[1,2,4] thiadiazol-5-yl-1H-benzimidazole

Using [1,2,4] thiadiazole-5-carboxylic acid synthesised by process in Reference Example 1, the title compound was obtained as a straw-coloured oily substance by the same process as in

Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD80D) δ : 6.42 (1H, s), 6.90-7.23 (5H, m), 7.39-7.50 (2H, m), 8.25-8.32 (2H, m), 8.86 (1H, s).

ESI-MS (m/e): 406 (M+H).

Example 107

4-(2,6-difluoro-phenoxy)-2-(pyrazine-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H- benzimidazole

2,6-difluoro phenol and 4-(methanesulphonyl) phenol were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 3.03 (3H, s), 6.28 (1H, s), 7.08 (1H, s), 7.17 (2H, d, J = 9.4 Hz), 7.19-7.24 (2H, m), 7.30-7.40 (1H, m), 7.93 (2H, d, J = 9.4 Hz), 8.70-8.75 (1H, m), 8.77-8.82 (1H, m), 9.55-9.60 (1H, m).

ESI-MS (m/e): 495 (M+H).

Example 108-1, 108-2

4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H- benzimidazole,
and

4-(2-methoxy-pyridine-3-yloxy)-2- pyridine-2-yl-6-(pyridine-3-yloxy)-1H- benzimidazole

3-hydroxy-2-methoxypyridine, 3-hydroxypyridine and picolinic acid were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was respectively obtained.

4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H- benzimidazole

¹H-NMR (CDCl₃) δ : 6.10-7.35 (8H, m), 7.77-7.84 (1H, m), 8.30-8.41 (3H, m), 8.53 (1H, d, J = 4.4 Hz).

ESI-MS (m/e): 398 (M+H).

4-(2-methoxy-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 3.95 and 3.99 (total 3H, each s), 6.25 and 6.45 (total 1H, each s), 6.80-7.45 (6H, m), 7.79-7.90 (1H, m), 8.00 (1H, d, J = 1.5 Hz), 8.30-8.63 (4H, m).

ESI-MS (m/e): 412 (M+H).

Example 109-1, 109-2

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-methoxy-pyridine-3-yloxy)-2-pyridine-2-yl-1H-

benzimidazole

and

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

3-hydroxy-2-methoxypyridine, 4-hydroxy-N,N-dimethylbenzamide and picolinic acid were successively used, and the title compound was respectively obtained by the same method as in Examples 108-1, 108-2, a process based on this or a combination of these with a normal procedure.

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-methoxy-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 3.03 and 3.08 (total 6H, each s), 3.95 and 4.00 (total 3H, each s), 6.27 and 6.47 (total 1H, each d, J = 1.8 Hz), 6.80-7.45 (8H, m), 7.80-7.91 (1H, m), 7.98-8.03 (1H, m), 8.38 and 8.48 (total 1H, each d, J = 7.8 Hz), 8.61 and 8.64 (total 1H, each d, J = 4.8 Hz)
ESI-MS (m/e): 482 (M+H).

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 3.03 and 3.08 (total 6H, each s), 6.18 and 6.23 (total 1H, each t, J = 7.0 Hz), 6.52 and 6.73 (total 1H, each d, J = 1.8 Hz), 6.80-7.42 (8H, m), 7.79 and 7.84 (total 1H, each t, J = 7.8 Hz), 8.37 and 8.40 (total 1H, each d, J = 7.8 Hz), 8.56 and 8.57 (total 1H, each d, J = 5.0 Hz).
ESI-MS (m/e): 468 (M+H).

Example 110

4-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole
ditrifluoroacetic acid salt

Using 4-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 78, and, by the same process as in Example 43, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 6.61 (1H, d, J = 2.0 Hz), 7.19 (1H, d, J = 8.0 Hz), 7.22 (1H, s), 7.31 (1H, td, J = 7.6Hz, 1.2 Hz), 7.48-7.60 (2H, m), 7.72-7.80 (1H, m), 7.83 (1H, dd, J = 7.6Hz, 1.2 Hz), 7.87-7.95 (1H, m), 8.03 (1H, td, J = 8.0Hz, 1.2 Hz), 8.01 (1H, dd, J = 7.6Hz, 1.2 Hz), 8.45 (1H, d, J = 5.2 Hz), 8.48-8.54 (1H, m), 8.76-8.84 (1H, m).
ESI-MS (m/e): 424 (M+H).

Example 111

4-(2-carbamoyl-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-cyano-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole obtained in Example 85, the title compound was obtained by the same process as in Example 110,

a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.99 (3H, s), 3.08 (3H, s), 6.56 (1H, s), 6.86-6.92 (1H, m), 6.95 (2H, J = 8.9 Hz), 7.04-7.08 (2H, m), 7.30-7.38 (4H, m), 7.36 (2H, d, J = 8.9 Hz), 7.52 (1H, d, J = 7.6 Hz), 7.80 (1H, t, J = 7.9 Hz), 8.36 (1H, d, J = 7.9 Hz), 8.52 (1H, d, J = 3.7 Hz).

ESI-MS (m/e): 494 (M+H).

Example 112

4-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-cyano-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole obtained in Example 85, the title compound was obtained by the same process as in Example 61, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.02 (3H, s), 3.16 (3H, s), 6.61 (1H, d, J = 2.0 Hz), 6.95 (1H, d, J = 2.0 Hz), 6.97 (2H, d, J = 8.6 Hz), 7.14-7.22 (2H, m), 7.38 (2H, d, J = 8.6 Hz), 7.52 (1H, dd, J = 4.9, 7.6 Hz), 7.56-7.62 (1H, m), 7.63-7.67 (1H, m), 7.97 (1H, dt, J = 1.6, 7.8 Hz), 8.48 (1H, d, J = 7.8 Hz), 8.68 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 509 (M+H).

Example 113

4-(2-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole obtained in Example 112, the title compound was obtained by the same process as in Example 64, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.70 (3H, s), 3.02 (3H, s), 3.15 (3H, s), 6.91 (1H, s), 7.04 (2H, d, J = 8.6 Hz), 7.30-7.38 (3H, m), 7.44 (2H, d, J = 8.6 Hz), 7.50-7.58 (2H, m), 7.95 (1H, d, J = 7.8 Hz), 8.02 (1H, t, J = 7.8 Hz), 8.63 (1H, d, J = 8.6 Hz), 8.71 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 533 (M+H).

Example 114

4-(2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-

1H-benzimidazole obtained in Example 112, the title compound was obtained by the same process as in Example 62, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.04 (3H, s), 3.15 (3H, s), 6.74 (1H, s), 6.99 (2H, d, J = 8.6 Hz), 7.10 (1H, s), 7.28-7.36 (2H, m), 7.44 (2H, d, J = 8.6 Hz), 7.50-7.58 (2H, m), 7.89 (1H, d, J = 7.8 Hz), 8.00-8.07 (1H, m), 8.56-8.64 (2H, m).

ESI-MS (m/e): 535 (M+H).

Example 115

4-(4-fluoro-phenoxy)-2-(pyrazol-1-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Step 1

Synthesis of 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazole-2-thiol

Carbon disulfide 0.06 ml and potassium hydroxide 54 mg were added to ethanol 2.0 ml solution of 3-(4-fluoro-phenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine 273 mg obtained in Example 68, and the reaction liquor was stirred at 80°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

Step 2

Synthesis of (4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazol-2-yl)-hydrazine

Hydrazine monohydrate 1.0 ml was added to 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazole-2-thiol 130 mg, and the reaction liquor was stirred at 130°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), hexane/ethyl acetate=1/1), and obtained the title compound.

Step 3

Production of 4-(4-fluoro-phenoxy)-2-(pyrazol-1-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

To ethanol 0.3 ml solution of (4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazol-2-yl)-hydrazine 8.3 mg was added tetramethoxy propane 0.012 ml, and the reaction liquor was stirred at 80°C overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol=9/1), and obtained the title compound.

¹H-NMR(CDCl₃) δ : 6.36 (1H, d, J = 2.6 Hz), 6.48-6.51 (2H, m), 6.77 (1H, d, J = 2.6 Hz), 7.05 (2H, d, J = 6.9 Hz), 7.11-7.18 (1H, m), 7.22-7.28 (2H, m), 7.72-7.75 (1H, m), 8.80-8.38 (2H, m), 8.48 (1H, d, J = 3.8 Hz).

ESI-MS (m/e): 388 (M+H).

Example 116

4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-2-[1,2,4] triazol-1-yl-1H-benzimidazole

Step 1

Synthesis of 4-(4-fluoro-phenoxy)-2-methyl sulphanyl-6-(pyridine-3-yloxy)-1H- benzimidazole

To dimethylformamide 1.0 ml solution of 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazole-2-thiol 78 mg synthesised in Example 115, potassium carbonate 30 mg and methyl iodide 0.014 ml were added, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

Step 2

Synthesis of 4-(4-fluoro-phenoxy)-2-methanesulphonyl-6- (pyridine-3-yloxy)-1H- benzimidazole

To chloroform 1.0 ml solution of 4-(4-fluoro-phenoxy)-2-methyl sulphanyl-6-(pyridine-3-yloxy)-1H-benzimidazole 80 mg was added metachloro perbenzoic acid 84 mg, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), ethyl acetate), and obtained the title compound.

Step 3

Production of 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy) -2-[1,2,4] triazol-1-yl-1H-benzimidazole

To dimethylformamide 0.5 ml solution of 4-(4-fluoro-phenoxy)-2-methanesulphonyl-6-(pyridine-3-yloxy)-1H-benzimidazole 16 mg was added sodium hydride 5.0 mg, and thereafter, [1,2,4]-triazole 10.4 mg was added, and the reaction liquor was stirred at 160°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer

chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), ethyl acetate), and the title compound was obtained.

¹H-NMR (CDCl₃) δ : 6.42 (1H, s), 7.03-7.15 (3H, m), 7.19 (1H, s), 7.27-7.32 (3H, m), 8.12 (1H, s), 8.32-8.38 (2H, m), 9.15 (1H, s).

ESI-MS (m/e): 389 (M+H).

Example 117

5-chloro-2-pyridine-2-yl-4,6-bis-(pyridine-3-yloxy)-1H-benzimidazole

Step 1

Synthesis of 3-chloro-2,4-bis (pyridine-3-yloxy)-nitrobenzene

To dimethylformamide 8 ml solution of [1,2,3]-trichloro-4-nitrobenzene 679 mg were added 3-hydroxypyridine 628 mg and potassium carbonate 1.82 g, and the reaction liquor was stirred at 100°C for two hours. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a straw-coloured oily substance.

Step 2

Synthesis of 3-chloro-2,4-bis (pyridine-3-yloxy) aniline

To suspension of 3-chloro-2,4-bis (pyridine-3-yloxy) nitrobenzene 1.2 g in methanol 15 ml and water 7.5 ml were added ammonium chloride 963 mg and iron powder 503 mg, and the reaction liquor was heated under reflux for three hours. The reaction liquor was eliminated by filtration, and next the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a straw-coloured oily substance.

Step 3

Synthesis of 3-chloro-2,4-bis (pyridine-3-yloxy)-6-nitroaniline

To 891 mg of 3-chloro-2,4-bis (pyridine-3-yloxy)-aniline dissolved in trifluoroacetic acid 20 ml was added potassium nitrate 315 mg, and the reaction liquor was stirred at room temperature overnight, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced

pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as orange color solid.

Step 4

Synthesis of 4-chloro-3,5-bis (pyridine-3-yloxy)-benzene-1,2-diamine

To suspension of 3-chloro-2,4-bis (pyridine-3-yloxy)-6-nitroaniline 143 mg in methanol 8 ml and water 4 ml were added ammonium chloride 128 mg and iron powder 67 mg, and the reaction liquor was heated under reflux for two hours. The reaction liquor was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as pale-brown solid.

Step 5

Production of 5-chloro-2-pyridine-2-yl-4,6-bis-(pyridine-3-yloxy)-1H-benzimidazole

4-chloro-3,5-bis (pyridine-3-yloxy)-benzene-1,2-diamine and picolinic acid were used, and it was synthesised in the same way as in Example 68, and the title compound was obtained as a straw-coloured solid.

¹H-NMR (DMSO-d₆) δ : 7.18-7.62 (6H, m), 7.92 and 7.99 (total 1H, each dt, J = 8.0, 1.8 Hz), 8.10-8.44 (5H, m), 8.66-8.72 (1H, m)

ESI-MS (m/e): 416, 418 (M+H).

Example 118

5-methyl-2-pyridine-2-yl-4,6-bis-(pyridine-3-yl-oxy)-1H-benzimidazole

Using 2,4-difluoro-3-methyl nitrobenzene synthesised by a process described in Chemical and Pharmaceutical Bulletin, 1982, vol.30, issue 10, pp.3530-3543, the title compound was obtained as pale yellow solid by the same process as in Example 117, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 2.03 and 2.10 (total 3H, each s), 7.01-7.50 (6H, m), 7.88 and 7.87 (total 1H, each dt, J = 7.7, 1.6 Hz), 8.06-8.41 (5H, m), 8.63-8.70 (1H, in).

ESI-MS (m/e): 396 (M+H).

Example 119

5-fluoro-2-pyridine-2-yl-4,6-bis-(pyridine-3-yloxy)-1H-benzimidazole

Using [1,2,3] trifluoro-4-nitrobenzene, the title compound was obtained as a straw-coloured solid by the same process as in Example 117, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 7.21-7.63 (6H, m), 7.90-8.01 (1H, m), 8.12-8.39 (3H, m), 8.43-8.50 (2H, m), 8.63-8.73 (1H, m)
ESI-MS (m/e): 400 (M+H).

Example 1204-(2-cyano-phenoxy)-6-(4-N,N-dimethylcarbamoyl-phenylsulfonyl)-2-pyridine-2-yl-1H-benzimidazole**Step 1**Synthesis of 5-(4-carboxy-phenyl sulphanyl)-3-(2-cyano phenoxy)-2-nitro-phenylamine

To dimethylformamide 2 ml solution of 3-(2-cyano phenoxy)-5-fluoro-2-nitro-phenylamine 47 mg obtained in Example 78 were added 4-mercaptobenzonic acid 31 mg and potassium carbonate 55 mg, and the reaction liquor was stirred at 60°C for two hours. The reaction liquor was concentrated, and trifluoroacetic acid 1 ml was added to the residue, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as orange colored solid.

Step 2Synthesis of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenyl sulphanyl)-2-nitro-phenylamine

To dichloromethane 2 ml solution of 5-(4-carboxy-phenyl sulphanyl)-3-(2-cyano phenoxy)-2-nitro-phenylamine 40 mg were added dimethylamine (2.0M tetrahydrofuran solution) 0.059 ml, 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 28 mg and N-hydroxybenzotriazole hydrate 20 mg, and the reaction liquor was stirred at room temperature for one hour 30 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as yellow powder.

Step 3Synthesis of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenyl sulphanyl)- benzene-1,2-diamine

To isopropyl alcohol 2 ml solution of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenyl sulphanyl)-2-nitro-phenylamine 32 mg were added electrolytic iron powder 19 mg and saturated ammonium chloride aqueous solution 0.2 ml, and the reaction liquor was heated under reflux for two hours. After eliminating the catalyst by filtration and eliminating the solvent by distillation,

the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

Step 4

Synthesis of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenylsulfonyl)-benzene-1,2-diamine

To dichloromethane 2 ml solution of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylaminocarbonyl-phenyl sulphanyl)-benzene-1,2-diamine 25 mg was added metachloroperbenzoic acid 38 mg, and the reaction liquor was stirred at room temperature for 15 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as yellow powder.

Step 5

Production of 4-(2-cyano-phenoxy)-6-(4-N,N-dimethylaminocarbonyl-phenylsulfonyl)-2-(pyridine-2-yl)-1H-benzimidazole

Using 3-(2-cyano phenoxy)-5-(4-N,N-dimethylaminocarbonyl-phenylsulfonyl)-benzene-1,2-diamine, the title compound was obtained as a brown solid by the same process as in Example 67 (Step 4), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.91 and 2.92 (total 3H, each s), 3.10 (3H, s), 6.99 (1H, m), 7.23-7.30 (1H, m), 7.39-7.46 (2H, m), 7.50-7.58 (3H, m), 7.68-7.78 (1H, m), 7.75 and 8.33 (total 1H, each s), 7.85 and 7.92 (total 1H, each t, J = 8.4 Hz), 7.95-8.20 (2H, m), 8.39 and 8.42 (total 1H, each d, J = 8.4 Hz), 8.63-8.67 (1H, m).

ESI-MS (m/e): 524 (M+H).

Example 121

1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3H-benzimidazole-5-yl)-pyrrolidin-1-yl)-ethanone

Step 1

Synthesis of 3-bromo-4-methoxymethoxy benzoic acid ethyl ester

To tetrahydrofuran 300 ml solution of 3-bromo-4-hydroxybenzoic acid ethyl ester 20.5 g synthesised using a process described in Monatsh. Chem. 22, 1901, 437 was added sodium hydride 5.5 g under ice cooling, and the reaction liquor was stirred for 30 minutes, and thereafter, chloromethyl methyl ether 10 ml was added to the reaction liquor at the same temperature, and

the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate and washed with water, thereafter the aqueous layer was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained solid was suspended in hexane, and the title compound was obtained as a white solid.

Step 2

Synthesis of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrole-1-carboxylic acid t-butyl ester

To dimethoxyethane 350 ml of 3-bromo-4-methoxymethoxy benzoic acid ethyl ester 21 g solution were added successively 1-(t-butoxy carbonyl) pyrrole-2-boron acid 21 g, tetrakis triphenylphosphine palladium 4.2 g and sodium carbonate aqueous solution (2M) 153 ml, and under a nitrogen atmosphere, the reaction liquor was heated under reflux overnight. After cooling, the reaction liquor was diluted with water, extracted with chloroform and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 12/1-10/1), and the title compound was obtained as a white solid.

Step 3

Synthesis of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester

5 % platinum carbon catalyst 8.2 g was added to ethanol 400 ml solution of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 28.4 g, and the reaction liquor was stirred under a hydrogen atmosphere for three days. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/6.5-1/6). and the title compound was obtained as a colourless oily substance.

Step 4

Synthesis of 3-(1-acetyl-pyrrolidin-2-yl)-4-hydroxybenzoic acid ethyl ester

To mixed solution of water 50 ml and ethanol 250 ml of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 26 g was added p-toluenesulfonic acid monohydrate 13 g, and the reaction liquor was heated under reflux for two days. After cooling, the reaction liquor was diluted with water, neutralized with aqueous sodium bicarbonate and extraction with chloroform-methanol mixture medium (10/1) were carried out, and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Acetic anhydride 13 ml

was added to pyridine 200 ml solution of the obtained crude product, and the mixture was stirred. One hour was allowed to pass, and acetic anhydride 6 ml was added. Pyridine 150 ml was added after 1 hour furthermore, and triethylamine 5 ml was added further 40 minutes later. Acetic anhydride 3 ml was added further 30 minutes later, and furthermore, the reaction liquor was stirred for 30 minutes. The reaction liquor was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried using anhydrous magnesium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To methanol 200 ml solution of the obtained crude product, potassium carbonate 10 g was added, and the reaction liquor was stirred at room temperature for four hours. The reaction liquor was concentrated down by distillation under reduced pressure, and the obtained residue was diluted with saturated ammonium chloride aqueous solution and extraction was carried out with ethyl acetate. It was dried using anhydrous magnesium sulphate, and next the solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid by recovering the obtained solid by filtration with acetic acid ethyl ester.

Step 5

Synthesis of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid ethyl ester

To dimethylformamide 100 ml solution of 3-(1-acetyl-pyrrolidin-2-yl)-4-hydroxybenzoic acid ethyl ester 12.4 g were added potassium carbonate 15 g, benzyl bromide 6.4 ml, and the reaction liquor was stirred at 50°C for one hour. The reaction liquor was cooled, and thereafter, it was diluted with saturated ammonium chloride aqueous solution and extraction was carried out with ethyl acetate. The organic layer was washed with water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 10/1-1/2-1/3), and the title compound was obtained as a yellow oily substance.

Step 6

Synthesis of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid

4 N sodium hydroxide aqueous solution 23 ml was added to ethanol 200 ml solution of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid ethyl ester 18.7 g, and the reaction liquor was stirred at room temperature overnight. 4 N sodium hydroxide aqueous solution 15 ml was further added to the reaction liquor, and the reaction liquor was stirred for seven hours. The reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was diluted with water and was washed with ether. The aqueous layer was acidified using 6 N hydrochloric acid and thereafter, it was extracted with chloroform and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid.

Step 7Synthesis of (3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy-phenyl)-carbamic acid t-butyl ester

Into a mixed solution of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid 5 g in toluene 15 ml and 2-methyl-2-propanol 15 ml were successively added diisopropyl ethylamine 3.0 ml and diphenylphosphoryl azide 3.8 ml and the reaction liquor was heated under reflux overnight. After cooling, saturated aqueous sodium chloride solution and saturated aqueous sodium bicarbonate were added to the reaction liquor and extraction with ethyl acetate was carried out, and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/0-1/1-0/1), and the title compound was obtained as colourless amorphous material.

Step 8Synthesis of 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone

To (3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy-phenyl)-carbamic acid t-butyl ester 4.1 g dissolved in trifluoroacetic acid 50 ml solution was added potassium nitrate 1.1 g, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and ice was added to the obtained residue, and thereafter, it was neutralized using ammonia water, and diluted with ethyl acetate. The precipitate was recovered by filtration, and crude product was obtained as a brown solid. The filtrate was diluted with saturated sodium chloride aqueous solution and was dried with anhydrous magnesium sulphate after extraction with acetic acid ethyl ester. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified using silica gel column chromatography (eluent: ethyl acetate) and the obtained solid was recovered by suspending in acetic acid ethyl ester, and crude product was obtained as brown solid. To ethanol 100 ml solution of the obtained crude product 2.8 g, hydrazine monohydrate 1.5 ml, expanded Raney nickel catalyst 1 g were added successively, and the reaction liquor was stirred at room temperature for three hours. The catalyst was eliminated by filtration by celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was diluted using saturated aqueous sodium bicarbonate and was dried with anhydrous magnesium sulphate after extraction with acetic acid ethyl ester. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform/methanol = 100/0-99/1-98/2-97/3-96/4-93/7), and the title compound was obtained as green amorphous material.

Step 9Synthesis of 1-(2-(6-benzyloxy-2-pyridine-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-

benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To toluene 43 ml solution of 1-(2-(4,5-diamino-2-benzyloxy-phenyl)- pyrrolidin-1-yl)-ethanone 1.39 g was added toluene solution 3 ml of pyridine-2-carboxaldehyde 460 mg, and the reaction liquor was stirred at room temperature. After two hours, pyridine-2-carboxaldehyde 46 mg was added, and the reaction liquor was stirred at 90°C for two hours. Moreover, pyridine-2-carboxaldehyde 46 mg was added, and the reaction liquor was stirred at 90°C for ten hours. After cooling, the precipitated solid was recovered by filtration, and crude product was obtained as a brown solid. To tetrahydrofuran 20 ml solution of the obtained crude product 1.1 g, sodium hydride 144 mg, 2-(chloromethoxy) ethyl trimethylsilane 667 mg were added, and the reaction liquor was stirred at room temperature for two hours 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquid and extraction with ethyl acetate was carried out and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: ethyl acetate), and the title compound was obtained as brown amorphous material.

Step 10Synthesis of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To ethanol 20 ml solution of 1.18 g of 1-(2-(6-benzyloxy-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone were added ammonium formate 713 mg, 20 % palladium hydroxide-carbon catalyst 119 mg, and the reaction liquor was heated under reflux for five hours. Ammonium formate 157 mg, 20 % palladium hydroxide-carbon catalyst 56 mg were added to the reaction liquor, and also the reaction liquor was heated under reflux for one hour. After cooling, catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was diluted with 1 N hydrochloric acid extracted with acetic acid ethyl ester and the extract dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform/methanol = 100/0-99/1-98/2), and the title compound was obtained as brown amorphous material.

Step 11Synthesis of 1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3-(2-trimethyl silyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To pyridine 1 ml solution of 29 mg of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethyl silyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone were added 5-(4-bromo-phenyl)-oxazole 30 mg, cesium carbonate 56 mg and copper (II) oxide 15 mg, and

the reaction liquor was stirred at 120°C in sealed tube overnight. After cooling, saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution were added successively to the reaction liquor, extraction was carried out ethyl acetate and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under the reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 12/1), and obtained the title compound as a yellow oily substance.

Step 12

Production of 1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 24 mg was dissolved in trifluoroacetic acid 1 ml, and the reaction liquor was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the title compound was obtained as a yellow oily substance.

¹H-NMR (CDCl₃) δ : 1.73-2.69 (7H, m), 3.54-3.91 (2H, m), 5.21-5.48 (1H, m), 6.91-7.98, 8.30-8.51, 8.57-8.73 (13H, each m).

ESI-MS (m/e): 466 (M+H).

Example 122

3-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

Using 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) and 3-cyano bromobenzene, the title compound was obtained as an oily substance by the same process as in Example 121 (Step 11) (Step 12), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.42 (7H, m), 3.56-3.93 (2H, m), 5.14-5.45 (1H, m), 6.91-7.73 (7H, m), 7.80-7.96 (1H, m), 8.30-8.43 (1H, m), 8.58-8.70 (1H, m), 10.58-10.82 (1H, m)

ESI-MS (m/e): 424 (M+H).

Example 123

3-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzamide

Using 3-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile obtained in Example 122, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.70-2.39 (7H, m), 3.39-3.89 (2H, m), 5.17-6.24 (3H, m), 6.97-7.92 (8H,

m), 8.26-8.42 (1H, m), 8.52-8.67 (1H, m), 10.42-10.72 (1H, m).

ESI-MS (m/e): 442 (M+H).

Example 124

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile

Using 5-bromo-pyridine-2-carbonitrile, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.50-2.42 (7H, m), 3.56-3.88 (2H, m), 5.09-5.40 (1H, m), 6.89-7.92 (6H, m), 8.26-8.70 (3H, m), 10.63-11.05 (1H, m).

ESI-MS (m/e): 425 (M+H).

Example 125

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carboxylic acid amide

Using 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile obtained in Example 124, the title compound was obtained as an oily substance by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.60-2.42 (7H, m), 3.42-3.90 (2H, m), 4.99-5.80 (2H, m), 6.74-8.67 (10H, m), 10.42-10.10.85 (1H, m).

ESI-MS (m/e): 443 (M+H).

Examples 126-1, 126-2

1-(2-(6-(5-bromo-pyridine-2-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

1-(2-(6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-bromo-2-methanesulphonyl-pyridine, the title compound was respectively obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

1-(2-(6-(5-bromo-pyridine-2-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

¹H-NMR (CDCl₃) δ : 1.50-2.40 (7H, m), 3.50-3.87 (2H, m), 5.03-5.14, 5.31-5.42 (1H, each m), 6.71-7.88, 10.48-11.15 (7H, each m), 8.08-8.40 (2H, m), 8.50-8.69 (1H, m).

ESI-MS (m/e): 478, 480 (M+H).

1-(2-(6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

n-1-yl)-ethanone

¹H-NMR (CDCl₃) δ : 1.57-2.59 (7H, m), 3.08-3.27 (3H, m), 3.57-3.89 (2H, m), 5.14-5.40 (1H, m), 6.94-7.64 (4H, m), 7.82-8.15 (2H, m), 8.33-8.75 (3H, m).

ESI-MS (m/e): 478 (M+H).

Example 1271-(2-(2-pyridine-2-yl-6-[quinoline-6-yloxy]-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-bromo-quinoline, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.67-2.69 (7H, m), 3.40-4.04 (2H, m), 5.25-5.63 (1H, m), 6.80-9.13 (12H, m), 10.22-11.44 (1H, br).

ESI-MS (m/e): 450 (M+H).

Example 1284-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-methyl-benzonitrile

Using 4-bromo-2-methyl-benzonitrile, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.48-2.54 (10H, m), 3.20-3.89 (2H, m), 5.06-5.41 (1H, m), 6.80-8.87 (10H, m).

ESI-MS (m/e): 438 (M+H).

Example 1291-(2-(2-pyridine-2-yl-6-(4-trifluoromethoxy-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-bromo-4-trifluoromethoxy-benzene, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.43-2.69 (7H, m), 3.32-3.91 (2H, m), 5.20-5.59 (1H, m), 6.23-8.97 (11H, m).

ESI-MS (m/e): 483 (M+H).

Example 1301-(2-(2-pyridine-2-yl-6-[quinoline-3-yloxy]-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 3-bromo-quinoline, the title compound was obtained as a yellow oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.00-2.47 (7H, m), 3.37-4.00 (2H, m), 5.26-5.54 (1H, m), 6.98-9.10 (12H, m), 10.44-10.73 (1H, m)
ESI-MS (m/e): 450 (M+H).

Example 131

1-(2-(6-(4-acetyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(4-iodo-phenyl)-ethanone, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.47-2.60 (10H, m), 3.52-3.88 (2H, m), 5.12-5.41 (1H, m), 6.97-7.74 (6H, m), 7.80-8.02 (3H, m), 8.30-8.44 (1H, m), 8.57-8.70 (1H, m).
ESI-MS (m/e): 441 (M+H).

Example 132

1-(2-(6-[biphenyl-4-yloxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-bromo-biphenyl, the title compound was obtained as a yellow oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.13-2.47 (7H, m), 3.40-3.91 (2H, m), 5.20-5.60 (1H, m), 6.72-7.89 (13H, m), 8.25-8.42 (1H, m), 8.42-8.67 (1H, m), 10.29-10.60 (1H, m).
ESI-MS (m/e): 475 (M+H).

Example 133

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N,N-dimethyl-benzenesulphonamide

Using 4-iodo-N,N-dimethyl-benzenesulphonamide, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.50-3.00 (13H, m), 3.40-3.92 (2H, m), 5.14-5.50 (1H, m), 6.40-8.80 (11H, m)
ESI-MS (m/e): 506 (M+H).

Example 134

1-(2-(6-[biphenyl-3-yloxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 3-bromo-biphenyl, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.80-2.50 (7H, m), 3.40-3.91 (2H, m), 5.20-5.60 (1H, m), 6.80-7.95 (13H, m)

m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 475 (M+H).

Example 135

1-(2-(6-(4-[propane-2-sulfonyl]-phenoxy)

2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-iodo-4-(propane-2-sulfonyl)-benzene, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.10-2.50 (13H, m), 3.05-3.30 (1H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 7.00-7.95 (8H, m), 8.30-8.50 (1H, m), 8.58-8.75 (1H, m), 10, 60-10.95 (1H, m).

ESI-MS (m/e): 505 (M+H).

Example 136

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzonitrile

Using 4-bromo-2-trifluoromethyl-benzonitrile, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.10-2.45 (7H, m), 3.50-3.95 (2H, m), 5.00-5.45 (1H, m), 6.60-7.95 (7H, m), 8.30-8.45 (1H, m), 8.55-8.75 (1H, m.), 10.80-11.60 (1H, m).

ESI-MS (m/e): 492 (M+H).

Examples 137-1, 137-2

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N-ethyl-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzonitrile obtained in Example 136, the title compounds were respectively obtained by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

¹H-NMR(CD₃OD) δ : 1.05-2.80 (7H, m), 3.50-4.20 (2H, m), 5.30-5.45 (1H, m), 7.30-7.80 (6H, m), 8.05-8.20 (1H, m), 8.20-8.38 (1H, m), 8.80-8.90 (1H, m).

ESI-MS (m/e): 510 (M+H).

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N-ethyl-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

¹H-NMR(CD₃OD) δ : 1.05-2.80 (10H, m), 3.60-4.05 (2H, m), 4.80-5.00 (2H, m), 5.30-5.45 (1H, m), 7.30-7.80 (5H, m), 8.05-8.20 (1H, m), 8.20-8.38 (1H, m), 8.80-8.90 (1H, m), 9.10-9.30 (1H, m).

ESI-MS (m/e): 538 (M+H).

Example 138

1-(2-(6-(4-[2-dimethylamino-ethoxy]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (2-(4-iodo-phenoxy)-ethyl)-dimethylamine, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.05-2.90 (13H, m), 3.00-4.45 (6H, m), 5.20-5.45 (1H, m), 6.80-8.00 (8H, m), 8.25-8.40 (1H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 486 (M+H).

Example 139

1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-bromo-benzylalcohol, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.68-2.40 (7H, m), 3.53-3.88 (2H, m), 4.62-4.72 (2H, m), 5.22-5.56 (1H, m), 6.82-7.62 (7H, m), 7.80-7.89 (1H, m), 8.32-8.40 (1H, m), 8.55-8.64 (1H, m).

ESI-MS (m/e): 429 (M+H).

Example 140

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N,N-dimethyl-benzamide

Using 4-bromobenzoic acid dimethyl amide, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.81-2.40 (7H, m), 2.98-3.17 (6H, m), 3.56-3.87 (2H, m), 5.20-5.53 (1H, m), 6.93-7.65 (7H, m), 7.81-7.89 (1H, m), 8.33-8.41 (1H, m), 8.60-8.67 (1H, m).

ESI-MS (m/e): 470 (M+H).

Example 1414-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N-methyl-benzamide

Using 4-bromo-N-methylbenzamide, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.39 (4H, m), 1.84 and 2.16 (total 3H, each s), 2.98-3.02 (3H, m), 3.58-3.74 (1H, m), 3.78-3.87 (1H, m), 5.16-5.43 (1H, m), 6.74-7.89 (8H, m), 8.36-8.39 (1H, m), 8.63-8.66 (1H, m).

ESI-MS (m/e): 456 (M+H).

Example 1421-(2-(2-pyridine-2-yl-6-(4-[pyrrolidine-1-carbonyl]-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (4-bromo-phenyl)-pyrrolidine-1-yl-methanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.40 (8H, m), 1.87 and 2.21 (total 3H, each s), 3.43-3.52 (2H, m), 3.60-3.71 (3H, m), 3.81-3.90 (1H, m), 5.21-5.50 (1H, m), 6.84-7.02 (2H, m), 7.25-7.58 (5H, m), 7.83-7.93 (1H, m), 8.36-8.45 (1H, m), 8.62-8.67 (1H, m).

ESI-MS (m/e): 496 (M+H).

Example 1431-(2-(6-(4-[morpholine-4-carbonyl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (4-bromo-phenyl)-morpholin-4-yl-methanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.78-2.62 (7H, m), 3.40-3.90 (10H, m), 5.23-5.50 (1H, m), 6.82-7.54 (7H, m), 7.86-7.94 (1H, m), 8.38-8.46 (1H, m), 8.64-8.69 (1H, m).

ESI-MS (m/e): 512 (M+H).

Example 1444-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy) benzoic acid • monotrifluoroacetic acid salt

Using 4-bromo-benzoic acid, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.86 and 2.10 (total 3H, each s), 1.92-2.48 (4H, m), 3.41-3.90 (2H, m), 5.36-5.39 (1H, m), 7.13-7.72 (5H, m), 8.00-8.07 (3H, m), 8.22-8.26 (1H, m), 8.73-8.80 (1H, m).
ESI-MS (m/e): 443 (M+H).

Example 145

1-(2-(6-(4-[piperidine-1-carbonyl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (4-bromo-phenyl)-piperidine-1-yl-methanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.45-2.40 (10H, m), 1.88 and 2.20 (total 3H, each s), 3.30-3.90 (6H, m), 5.23-5.53 (1H, m), 6.83-7.55 (7H, m), 7.84-7.94 (1H, m), 8.37-8.46 (1H, m), 8.63-8.68 (1H, m).
ESI-MS (m/e): 510 (M+H).

Example 146

1-(2-(6-(4-[4-acetyl-piperazine-1-carbonyl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(4-(4-bromo-benzoyl)-piperazine-1-yl)-ethanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.84-2.40 (10H, m), 3.24-3.88 (10H, m), 5.22-5.48 (1H, m), 6.94-7.09 (2H, m), 7.22-7.48 (5H, m), 7.84-7.93 (1H, m), 8.37-8.43 (1H, m), 8.63-8.66 (1H, m) ESI-MS (m/e): 553 (M+H).

Example 147

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

Step 1

Synthesis of 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silanyl-ethoxymethyl)-1H-benzimidazol-5-yloxy)-benzonitrile

To N-methyl-pyrrolidinone 1 ml solution of 4-fluoro cyanobenzene 20 mg and 30 mg of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) was added sodium hydride 5.8 mg, and the reaction liquor was stirred at 100°C in sealed tube overnight. After cooling, saturated aqueous sodium bicarbonate was added to the reaction liquid and extraction with ethyl acetate was carried out, and the organic layer was washed with water and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by thin layer chromatography fractionation and recovery (Kieselgel™ 60F₂₅₄, Art 5744 (Merck Co.), chloroform/methanol = 9/1), and obtained the title compound as a yellow oily

substance.

Step 2

Production of 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silanyl- ethoxymethyl)-1H-benzimidazol-5-yloxy)-benzonitrile, the title compound was obtained as an oily substance by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.52-2.42 (7H, m), 3.42-3.92 (2H, m), 5.02-5.40 (1H, m), 6.77-7.75 (7H, m), 7.75-7.94 (1H, m), 8.20-8.46 (1H, m), 8.50-8.69 (1H, m), 10.67-11.06 (1H, m).

ESI-MS (m/e): 424 (M+H).

Example 148

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzamide

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)- benzonitrile obtained in Example 147, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.05-2.40 (7H, m), 3.43-3.89 (2H, m), 5.10-6.32 (3H, m), 6.88-7.90 (8H, m), 8.27-8.42 (1H, m), 8.53-8.68 (1H, m), 10.47-11.80 (1H, m).

ESI-MS (m/e): 442 (M+H).

Example 149

2-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

Using 2-fluoro-benzonitrile, the title compound was obtained as an oily substance by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.50-2.49 (7H, m), 3.43-3.89 (2H, m), 5.10-5.34 (1H, m), 6.83-7.92 (8H, m), 8.31-8.42 (1H, m), 8.53-8.68 (1H, m), 10.80-11.23 (1H, m).

ESI-MS (m/e): 424 (M+H).

Example 150

2-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzamide

Using 2-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)- benzonitrile obtained in Example 149, the title compound was obtained as an oily substance by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.52-2.46 (7H, m), 3.43-3.91 (2H, m), 5.10-5.51 (1H, m), 5.99 (1H, brs),

6.72-7.98 (8H, m), 8.26-8.43 (2H, m), 8.59-8.70 (1H, m), 10.58-10.94 (1H, m).

ESI-MS (m/e): 442 (M+H).

Example 151

1-(2-(6-(4-nitro-phenoxy)-2-pyridine-2-yl-3H-benzimidazole-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluoro-nitrobenzene, the title compound was obtained by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.40-2.50 (7H, m), 3.50-3.95, (2H, m), 5.05-5.40 (1H, m), 7.00-7.80 (5H, m), 7.80-7.95 (1H, m), 8.15-8.30 (2H, m), 8.30-8.45 (1H, m), 8.60-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 444 (M+H).

Example 152

1-(2-(2-pyridine-2-yl-6-(4-[2H-tetrazol-5-yl]-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole-5-yloxy)-benzonitrile obtained in Example 147 (Step 1), the title compound was obtained by the same process as in Example 60 and Example 121 (Step 12), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.51-2.58 (7H, m), 3.43-3.90 (2H, M), 5.09-5.55 (1H, m), 6.73-7.60, 7.69-8.04, 8.29-8.69 (10H, each m).

ESI-MS (m/e): 467 (M+H).

Example 153

1-(2-(6-(4-[5-methyl-[1,2,4]oxadiazol-3-yl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-phenyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-5-yloxy)-benzonitrile obtained in Example 147 (Step 1), the title compound was obtained by the same process as in Example 61, Example 64 and Example 121 (Step 12), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.49-2.7 (10H, m), 3.39-3.90 (2H, m), 5.17-5.52 (1H, m), 6.26-8.89 (11H, m).

ESI-MS (m/e): 481 (M+H).

Example 154

3-(4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-phenyl)-4H-[1,2,4]

oxadiazole-5-one

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethylsilyl-ethoxymethyl) -1H-benzimidazol-5-yloxy)-benzonitrile obtained in Example 147 (Step 1), the title compound was obtained by the same process as in Example 61, Example 62 and Example 121 (Step 12), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.82-2.47 (7H, m), 3.60-3.3.94 (2H, m), 5.24-5.43 (1H, m), 7.15-8.05 (8H, m), 8.23-8.31 (1H, m), 8.71-8.78 (1H, m)

ESI-MS (m/e): 483 (M+H).

Example 1555-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-1,3-dihydro-benzimidazole-2-one**Step 1**Synthesis of 1-(2-(6-[3,4-dinitro-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluoro-1,2-dinitro-benzene, the title compound was obtained as red oily substance by the same process as in Example 147 (Step 1), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.80-2.57 (7H, m), 3.61-4.02 (2H, m), 5.27-5.60 (1H, m), 6.77-7.60 (6H, m), 7.91-8.06 (1H, m), 8.17-8.33 (1H, m), 8.72 (1H, brs).

ESI-MS (m/e): 455 (M+H).

Step 2Synthesis of 1-(2-(6-[3,4-diamino-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To ethanol 1 ml solution of 72 mg of 1-(2-(6-[3,4-dinitro-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone were added hydrazine monohydrate 0.030 ml, expanded Raney nickel catalyst 20 mg, and the reaction liquor was stirred at room temperature for two hours. The catalyst was eliminated by filtration by celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 9/1), and obtained the title compound as brown oily substance.

Step 3Synthesis of 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silyl-ethoxymethyl)-1H-benzimidazol-5-yloxy)-1,3-dihydro-benzimidazole-2-one

Using 1-(2-(6-[3,4-diamino-phenoxy]-2-pyridine-2-yl-3-(2-trimethyl silyl-ethoxymethyl) -3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone, the title compound was obtained as brown oily

substance by the same process as in Example 62, a process based on this or a combination of these with a normal procedure.

Step 4

Production of 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-1,3-dihydrobenzimidazole-2-one

Using 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silanyl-ethoxymethyl)-1H-benzimidazol-5-yloxy)-1,3-dihydro-benzimidazole-2-one, the title compound was obtained as amorphous material by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.57 (7H, m), 3.61-4.02 (2H, m), 5.27-5.60 (1H, m), 6.77-7.60 (6H, m), 7.91-8.06 (1H, m), 8.17-8.33 (1H, m), 8.72 (1H, brs).

ESI-MS (m/e): 455 (M+H).

Example 156

1-(2-(6-[3H-benzimidazol-5-yloxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

1-(2-(6-[3,4-diamino-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 155 (Step 2) 19 mg was dissolved in formic acid 1 ml, and the reaction liquor was stirred at 100°C for two hours. The reaction liquor was concentrated under reduced pressure, and the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.80-2.2.55 (7H, m), 3.60-4.00 (2H, m), 5.33-5.69 (1H, m), 7.00-7.80, 7.91-8.04, 8.16-8.30, 8.67-8.80 (10H, each m).

ESI-MS (m/e): 439 (M+H).

Example 157

1-(2-(6-(2-methyl-3H-benzimidazol-5-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using acetic acid, the title compound was obtained by the same process as in Example 156, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.69-2.63 (10H, m), 3.42-3.91 (2H, m), 5.20-5.64 (1H, m), 6.58-7.87 (9H, m), 8.22-8.66 (2H, m).

ESI-MS (m/e): 453 (M+H).

Example 158

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyrimidine-2-carbonitr

ile

Using 5-bromo-pyrimidine-2-carbonitrile, the title compound was obtained as a white solid by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.81-2.40 (7H, m), 3.56-3.88 (2H, m), 5.08-5.34 (1H, m), 6.75-7.70 (3H, m), 7.81-7.90 (1H, m), 8.33-8.63 (4H, m).

ESI-MS (m/e): 426 (M+H).

Example 159

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyrimidine-2-carboxamide

Using 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyrimidine-2-carbonitrile obtained in Example 158, it was obtained as a white solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.79-2.42 (7H, m), 3.60-3.90 (2H, m), 5.18-5.39 (1H, m), 6.99-7.71 (3H, m), 7.82-7.92 (1H, m), 8.34-8.42 (1H, m), 8.55-8.65 (3H, m).

ESI-MS (m/e): 444 (M+H).

Example 160

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy) benzoic acid ethyl ester

Using 4-fluorobenzoic acid ethyl ester, it was obtained as a white solid by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.24-1.41 (3H, m), 1.70-2.38 (7H, m), 3.53-3.87 (2H, m), 4.32-4.41 (2H, m), 5.14-5.45 (1H, m), 6.96-7.67 (5H, m), 7.82-7.91 (1H, m), 7.98-8.06 (2H, m), 8.34-8.43 (1H, m), 8.61-8.68 (1H, m).

ESI-MS (m/e): 471 (M+H).

Example 161

1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Step 1

Synthesis of 1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To tetrahydrofuran 1 ml solution of 29.2 mg of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) were added successively diisopropylamine 0.019 ml, triphenyl phosphine 27.6 mg, 2-phenyl-ethanol 0.011 ml, and the

reaction liquor was stirred at room temperature for six hours. Diisopropylamine 0.040 ml, triphenyl phosphine 53.2 mg, 2-phenyl-ethanol 0.023 ml were added successively to the reaction liquor, and the reaction liquor was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquor, extracted with acetic acid ethyl ester and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), ethyl acetate), and obtained the title compound as brown oily substance.

Step 2

Production of 1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone, the title compound was obtained as an oily substance by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ 1.59-2.23 (7H, m), 2.87-3.10, 3.50-3.86, 3.96-4.35 (6H, each m), 5.04-5.13, 5.46-5.57 (1H, each m), 6.53-7.55 (8H, m), 7.77-7.89 (1H, m), 8.32-8.40 (1H, m), 8.54-8.65 (1H, m), 10.73-11.14 (1H, m)

ESI-MS (m/e): 4271 (M+H).

Example 162

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Step 1

Synthesis of 2-(2-(4-fluoro-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester

To a mixed solution of 3-bromo-4-fluoro-nitrobenzene 4.3 g, dimethoxyethane 130 ml of 1-(t-butoxy carbonyl) pyrrole-2-boron acid 5.0 g and water 22 ml, tetrakis triphenylphosphine palladium 1.1 g, sodium carbonate 4.2 g were added and the reaction liquor was heated under reflux overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquid and the liquid was extracted with ethyl acetate, and the organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane/ethyl acetate = 20/1), and the title compound was obtained as a yellow oily substance.

Step 2

Synthesis of 2-((2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1-carboxylic acid

t-butyl ester

To 2-(2-fluoro-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 2.5 g and 4-methanesulphonyl-phenol 1.55 g dissolved in dimethylformamide 20 ml was added potassium carbonate 3.38 g, and the reaction liquor was stirred at 100°C for two hours. After cooling, water was added to the reaction liquid and the liquid was extracted with ethyl acetate, washed with water and saturated aqueous sodium chloride solution, and the organic layer was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1), and the title compound was obtained as a straw-coloured solid.

Step 3Synthesis of 2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester

To ethanol solution 120 ml of 2-((2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 2.87 g was added 5 % platinum carbon catalyst 1.0 g, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a white solid.

Step 4Synthesis of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone

Zinc powder 342 mg and chloroformic acid benzyl ester 650 mg were added to benzene 25 ml solution of 2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 1.51g, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was filtered with celite, and saturated aqueous sodium bicarbonate was added to filtrate, extracted with ethyl acetate, and the organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained crude product was dissolved in 4 N hydrochloric acid-1,4-dioxane 20 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the obtained crude product was dissolved in chloroform 30 ml, and pyridine 2 ml and anhydrous trifluoroacetic acid 0.5 ml were added under ice cooling, and the reaction liquor was stirred at room temperature for two hours. 1 N hydrochloric acid was added to the reaction liquid and the liquid was extracted with ethyl acetate, and washed with water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and

the organic layer was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and 10 % palladium-carbon catalyst 50 mg was added to methanol 100 ml solution of the obtained crude product, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-1/3), and the title compound was obtained as a white solid.

Step 5

Synthesis of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-4-nitro-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone

To trifluoroacetic acid 2 ml solution of 588 mg of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone was added potassium nitrate 153 mg, and the reaction liquor was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and it was neutralized and thereafter, it was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained as yellow solid.

Step 6

Synthesis of 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To ethanol 10 ml solution of 521 mg of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-4-nitro-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone was added expanded Raney nickel catalyst 100 mg, and under a hydrogen atmosphere, the reaction liquor was stirred overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To methanol 10 ml solution of the obtained crude product 448 mg, pyridine-2-carboxaldehyde 226 mg was added, and the reaction liquor was stirred at 50°C overnight.

Water was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform / methanol = 20/1), and the title compound was obtained as a straw-coloured solid.

Step 7**Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole**

To mixed solution of water 3 ml and methanol 16 ml of 375 mg 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone was added potassium carbonate 500 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was concentrated down by distillation under reduced pressure, and saturated aqueous sodium bicarbonate was added and diluted, and thereafter, it was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate.

The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform / methanol / ammonia water = 10/1/0.1), and the title compound was obtained as a straw-coloured solid.

Step 8**Production of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**

To methylene chloride 1 ml solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole 10 mg, acetic anhydride 0.003 ml was added, and thereafter the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 1.60-2.40 (7H, m), 3.05 and 3.08 (total 3H, each s), 3.52-3.90 (2H, m), 5.13-5.37 (1H, m), 7.08-7.69 (5H, m), 7.83-7.97 (3H, m), 8.32-8.40 (1H, m), 8.61-8.70 (1H, m).

ESI-MS (m/e): 477 (M+H).

Example 163**1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B**

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol 230 mg obtained in Example 162 (Step 7) was optically-resolved using a column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / 2-propanol / diethylamine 20/80/0.1, flow rate: 10 ml/min), and enantiomer A (retention time: 19.0 min), enantiomer B (retention time: 32.2 min) were respectively obtained as yellow oily substance.

Example 1641-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone A

To methylene chloride 1 ml solution of 12 mg of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A obtained in Example 163 was added acetic anhydride 0.003 ml, and thereafter the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound, one of chiral body was obtained as a white solid.

¹H-NMR (CDCl₃) δ : 1.60-2.40 (7H, m), 3.05 and 3.08 (total 3H, each s), 3.52-3.90 (2H, m), 5.13-5.37 (1H, m), 7.08-7.69 (5H, m), 7.83-7.97 (3H, m), 8.35-8.43 (1H, m), 8.61-8.70 (1H, m).

ESI-MS (m/e): 477 (M+H).

Specific rotation: $[\alpha]^{24}_D$ (c = 0.100, ethanol) -46.9°C.

Example 1651-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone B

To methylene chloride 1 ml solution of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B 44 mg obtained in Example 163 was added acetic anhydride 0.011 ml, and thereafter the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound, one of chiral body as a white solid.

ESI-MS (m/e): 477 (M+H).

Specific rotation: $[\alpha]^{24}_D$ (c = 0.100, ethanol) +47.7°C.

Example 1662,2,2-trifluoro-1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluorophenol, the title compound was obtained as a white solid by process same as in Example 162 (Step 2)-(Step 6), a process based on these or combining these and the normal method.

¹H-NMR (CDCl₃) δ : 1.96-2.21 (3H, m), 2.31-2.43 (1H, m), 3.77-4.08 (2H, m), 5.47-5.70 (1H, m), 6.88-6.91 (1H, m), 7.00-7.08 (4H, m), 7.26-7.50 (2H, m), 7.82-7.85 (1H, m), 8.31-8.35 (1H,

m), 8.57-8.61 (1H, m).

ESI-MS (m/e): 471 (M+H).

Example 167

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluorophenol, the title compound was obtained as a white solid by process same as in Example 162 (Step 2)-(Step 8), a process based on these or combining these and the normal method.

¹H-NMR (CDCl₃) δ : 1.83-2.03 (6H, m), 2.32-2.41 (1H, m), 3.58-3.86 (2H, m), 5.26-5.57 (1H, m), 6.96-7.06 (5H, m), 7.24-7.35 (2H, m), 7.80-7.88 (1H, m), 8.30-8.37 (1H, m), 8.56-8.62 (1H, m).

ESI-MS (m/e): 417 (M+H).

Example 168

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-hydroxy-ethanone

Using 4-fluorophenol, to chloroform 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same process as in Example 162 (Step 2)-(Step 7) were added successively glycolic acid 4.5 mg, N-hydroxybenzotriazole hydrate 12.3 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 15.4 mg, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound.

¹H-NMR (CDCl₃) δ : 1.88-2.13 (3H, m), 2.20-2.43 (1H, m), 3.40-4.21 (4H, m), 5.14-5.60 (1H, m), 6.85-7.54 (7H, m), 7.78-7.86 (1H, m), 8.29-8.37 (1H, m), 8.56-8.61 (1H, m).

ESI-MS (m/e): 433 (M+H).

Example 169

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methoxy-ethanone

Using methoxyacetic acid, it was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.41 (4H, m), 3.26-3.46 (3H, m), 3.52-4.16 (4H, m), 5.28-5.60 (1H, m), 6.79-7.57 (7H, m), 7.77-7.85 (1H, m), 8.28-8.38 (1H, m), 8.56-8.62 (1H, m)

ESI-MS (m/e): 447 (M+H).

Example 170

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-phenyl-propanone

pane-1-one

Using 3-phenyl-propionic acid, it was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.82-3.03 (8H, m), 3.48-3.93 (2H, m), 5.13-5.99 (1H, m), 6.82-7.60 (12H, m), 7.80-7.08 (1H, m), 8.09-8.39 (1H, m), 8.56-8.66 (1H, m).

ESI-MS (m/e): 507 (M+H).

Example 171(2-(6-[4-fluoro-phenoxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-(2R)-pyrrolidine-2-yl-methanone

To chloroform 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively 1-t-butoxy carbonyl-D-proline 13.8 mg, N-hydroxybenzotriazole hydrate 12.3 mg and 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride 15.4 mg, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and thereafter the obtained residue was dissolved in 4 N hydrochloric acid-ethyl acetate solution 1 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by thin layer chromatography (NH TLC plate (FUJI SILYSIA CHEMICAL Co.), chloroform /methanol = 30/1), and the title compound was obtained as oily substance.

¹H-NMR (CDCl₃) δ : 0.82-4.00 (13H, m), 5.23-5.61 (1H, m), 6.82-7.59 (7H, m), 7.78-7.88 (1H, m), 8.32-8.39 (1H, m), 8.57-8.64 (1H, m).

ESI-MS (m/e): 472 (M+H).

Example 172(2-(6-[4-fluoro-phenoxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-(2S)-pyrrolidine-2-yl-methanone

Using 1-t-butoxycarbonyl-L-proline, the title compound was obtained as oily substance by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.82-4.00 (13H, m), 5.23-5.61 (1H, m), 6.82-7.59 (7H, m), 7.78-7.88 (1H, m), 8.30-8.39 (1H, m), 8.57-8.64 (1H, m).

ESI-MS (m/e): 472 (M+H).

Example 1732-dimethylamino-1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using N,N-dimethylglycine hydrochloride, it was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.81-2.57 (10H, m), 2.76-3.96 (4H, m), 5.41-5.62 (1H, m), 6.94-7.37 (7H, m), 7.81-7.89 (1H, m), 8.33-8.38 (1H, m), 8.59-8.68 (1H, m).

ESI-MS (m/e): 460 (M+H).

Example 174

1-(2-(6-[4-fluoro-phenoxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-propane-1-one

Using propionic acid, the title compound was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.95-1.24 (3H, m), 1.70-2.60 (6H, m), 3.52-3.94 (2H, m), 5.24-5.62 (1H, m), 6.75-7.66 (7H, m), 7.77-7.92 (1H, m), 8.27-8.44 (1H, m), 8.52-8.68 (1H, m), 10.66-11.08 (1H, m)

ESI-MS (m/e): 431 (M+H).

Example 175

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-butane-1-one

Using n-butyric acid, the title compound was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.70-1.07 (3H, m), 1.40-2.44 (8H, m), 3.53-3.91 (2H, m), 5.25-5.60 (1H, m), 6.72-7.66 (7H, m), 7.80-7.93 (1H, m), 8.30-8.44 (1H, m), 8.53-8.68 (1H, m), 10.68-11.18 (1H, m).

ESI-MS (m/e): 445 (M+H).

Example 176

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-hydroxy-propane-1-one

Using 3-hydroxypropionic acid, the title compound was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.43-2.73 (6H, m), 3.24-4.27 (5H, m), 5.24-5.60 (1H, m), 6.75-7.60 (7H, m), 7.76-7.88 (1H, m), 8.27-8.40 (1H, m), 8.53-8.66 (1H, m), 10.44-11.01 (1H, m).

ESI-MS (m/e): 447 (M+H).

Example 177

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylami

no-ethanone

Using N-t-butoxycarbonyl-N-methylglycine, the title compound was obtained by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.82-2.01 (3H, m), 2.43-2.56 (4H, m), 3.25-4.15 (4H, m), 5.32-5.37 (1H, m), 7.00-7.31 (4H, m), 7.38-7.58 (2H, m), 8.03-8.08 (1H, m), 8.37-8.43 (1H, m), 8.69-8.79 (1H, m), 8.80-8.94 (1H, m).

ESI-MS (m/e): 446 (M+H).

Example 1785-(4-fluoro-phenoxy)-6-(1-methansulphonyl-pyrrolidine-2-yl)-2-pyridine-2-yl-1H-benzimidazole

To ethyl acetate 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively triethylamine 0.01 ml and methane sulphonyl chloride 0.005 ml, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 1.80-2.08 (3H, m), 2.28-2.42 (1H, m), 2.81 and 2.84 (total 3H, each s), 3.47-3.74 (2H, m), 5.17-5.37 (1H, m), 6.79-7.93 (8H, m), 8.30-8.37 (1H, m), 8.57-8.61 (1H, m).

ESI-MS (m/e): 453 (M+H).

Example 1795-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-(1-pyrimidine-2-yl-pyrrolidin-2-yl)-1H-benzimidazole

To ethanol 2 ml solution of 17.1 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively triethylamine 0.013 ml and 2-chloro-pyrimidine 6.3 mg, and the reaction liquor was heated under reflux for three hours. The reaction solvent was eliminated by distillation under reduced pressure, and next, the obtained residue was refined by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the obtained fraction was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, and thereafter, was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as white individual(sic).

¹H-NMR (CDCl₃) δ : 1.98-2.15 (3H, m), 2.34-2.42 (1H, m), 3.68-3.78 (1H, m), 3.90-4.07 (1H, m), 5.63 (1H, d, J = 8.0 Hz), 6.43 (1H, brs), 6.87-7.55 (7H, m), 7.79-7.84 (1H, m), 8.15-8.34 (3H, m), 8.55-8.58 (1H, m).

ESI-MS (m/e): 453 (M+H).

Example 180

2-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-acetamide

To acetonitrile 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively potassium carbonate 11.4 mg and iodoacetamide 11.1 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was concentrated, thereafter the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid) and the obtained fraction was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as white individual(sic).

¹H-NMR (CDCl₃) δ : 1.60-2.04 (3H, m), 2.20-2.13 (1H, m), 2.80-2.85 (1H, m), 3.37-3.44 (2H, m), 3.96-4.03 (1H, m), 5.41-5.52 (1H, m), 6.90-7.34 (5H, m), 7.36-7.39 (1H, m), 7.65 and 8.00 (total 1H, each s), 7.83-7.87 (1H, m), 8.36-8.39 (1H, m), 8.59-8.64 (1H, m).

ESI-MS (m/e): 432 (M+H).

Example 181

2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid ethyl ester

To benzene 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively zinc powder 5.2 mg and ethyl chloroformate 0.006 ml, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 1.23-1.31 (3H, m), 1.80-2.00 (3H, m), 2.20-2.39 (1H, m), 3.50-3.79 (2H, m), 3.91-4.17 (2H, m), 5.17-5.38 (1H, m), 6.81-7.63 (7H, m), 7.77-7.85 (1H, m), 8.28-8.39 (1H, m), 8.55-8.63 (1H, m).

ESI-MS (m/e): 447 (M+H).

Example 182

2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide

To methylene chloride 1 ml solution of 17.1 mg of

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) were added successively dimethylamino pyridine 5 mg and isocyanic acid trimethylsilyl ester 0.029 ml, and the reaction liquor was stirred at room temperature overnight. Water was added to the reaction liquid and the liquid was extracted with ethyl acetate and thereafter, was washed with saturated aqueous sodium chloride solution. After drying and concentration, the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid) and the obtained fraction was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid.

¹H-NMR (CDCl₃) δ : 1.83-2.09 (3H, m), 2.22-2.40 (1H, m), 3.07 (3H, s), 3.56-3.82 (2H, m), 4.35 and 4.62 (total 2H, each brs), 5.01-5.20 (1H, m), 7.08-7.95 (8H, m), 8.34-8.40 (1H, m), 8.62-8.64 (1H, m).

ESI-MS (m/e): 478 (M+H).

Examples 183-1, 183-2

2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide enantiomer A and enantiomer B

The racemic body 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide 10 mg obtained in Example 182 was optically-resolved using a column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane/ ethanol 20/80, flow rate: 10 ml/min), and enantiomer A (retention time: 17.9 min), enantiomer B (retention time: 27.6 min) were respectively obtained as white solid.

Enantiomer A.

ESI-MS (m/e): 478 (M+H).

Specific rotation: $[\alpha]^{24}_D$ (c = 0.100, ethanol) -27.4°C.

Enantiomer B.

ESI-MS (m/e): 478 (M+H).

Specific rotation: $[\alpha]^{24}_D$ (c = 0.100, ethanol) +28.4°C.

Example 184

2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide

To methylene chloride 1 ml solution of 31.2 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example

168 were added successively dimethylaminopyridine 2 mg and isocyanic acid trimethylsilyl ester 0.059 ml, and the reaction liquor was stirred at room temperature overnight. Water was added to the reaction liquid and the liquid was extracted with ethyl acetate and thereafter the extract washed with saturated aqueous sodium chloride solution. After drying and concentration, the obtained residue was refined by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 1.88-2.08 (3H, m), 2.32-2.48 (1H, m), 3.62-3.87 (2H, m), 4.34 and 4.71 (total 2H, each brs), 5.15-5.30 (1H, m), 6.91-7.73 (7H, m), 7.81-7.87 (1H, m), 8.31-8.37 (1H, m), 8.59-8.61 (1H, m).

ESI-MS (m/e): 418 (M+H).

Examples 185-1, 185-2

2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide enantiomer A and enantiomer B

The racemic body 2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide 9.0 mg obtained in Example 184 was optically-resolved by a column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / 2-propanol 50/50, flow rate: 10 ml/min), and enantiomer A (retention time: 12.1 min), enantiomer B (retention time: 26.9 min) were respectively obtained as white solid.

Enantiomer A.

ESI-MS (m/e): 418 (M+H).

Enantiomer B.

ESI-MS (m/e): 418 (M+H).

Example 186

2-(6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide

Using 4-hydroxy-N,N-dimethyl-benzamide, the title compound was obtained as a white solid by the same process as in Example 162 (Step 2)-(Step 7) and Example 182, a process based on these or a combination of these with a normal procedure..

¹H-NMR (CDCl₃) δ : 1.85-2.07 (3H, m), 2.28-2.43 (1H, m), 3.00-3.18 (6H, m), 3.60-3.80 (2H, m), 5.10-5.23 (1H, m), 7.01-7.76 (7H, m), 7.83-7.88 (1H, m), 8.33-8.39 (1H, m), 8.63-8.64 (1H, m).

ESI-MS (m/e): 471 (M+H).

Examples 187-1, 187-2**2-(6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide enantiomer A and enantiomer B**

2-(6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide 72.2 mg of racemic body obtained in Example 186 was optically-resolved by a column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol 40/60, flow rate: 10 ml/min), and enantiomer A (retention time: 18.1 min), enantiomer B (retention time: 23.9 min) were respectively obtained as white solid.

Enantiomer A.

ESI-MS (m/e): 471 (M+H).

Enantiomer B.

ESI-MS (m/e): 471 (M+H).

Example 188**2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid ethyl ester amide**

Using isocyanic acid ethyl ester, the title compound was obtained as a white solid by the same process as in Example 184, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.94-1.07 (3H, m), 1.80-2.03 (3H, m), 2.25-2.41 (1H, m), 3.10-3.26 (2H, m), 3.57-3.74 (2H, m), 4.02-4.14 (1H, m), 5.07-5.23 (1H, m), 6.85-7.66 (7H, m), 7.78-7.85 (1H, m), 8.30-8.38 (1H, m), 8.54-8.63 (1H, m).

ESI-MS (m/e): 446 (M+H).

Example 189**1-(2-(6-(4-fluoro-phenoxy)-2-pyrazine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**

Using pyrazine-2-carboxaldehyde, the title compound was obtained as a white solid by the same process as in Example 162 (Step 6)-(Step 8), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.86-2.08 (7H, m), 3.37-3.90 (2H, m), 5.27-5.55 (1H, m), 6.76-7.64 (6H, m), 8.32-8.62 (2H, m), 9.53-9.56 (1H, m).

ESI-MS (m/e): 418 (M+H).

Example 190**1-(2-(6-(4-fluoro-phenoxy)-2-thiazol-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**

Using thiazole-2-carboxaldehyde, it was obtained as a white solid by the same process as in Example 162 (Step 6)-(Step 8), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.23 (6H, m), 2.24-2.43 (1H, m), 3.50-3.88 (2H, m), 5.28-5.57 (1H, m), 6.64-7.62 (7H, m), 7.89-7.94 (1H, m).

ESI-MS (m/e): 423 (M+H).

Example 191

1-(6-[4-methanesulphonyl-phenoxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-methanol

Using D,L-prolinol, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.64-1.92 (3H, m), 1.97-2.06 (1H, m), 3.00-3.12 (1H, m), 3.04 (3H, s), 3.38-3.46 (1H, m), 3.53-3.64 (2H, m), 3.84 (1H, brs), 6.98 (2H, d, J = 8.6 Hz), 7.10 and 7.22 (total 1H, each s), 7.33-7.40 (1H, m), 7.50-7.57 (1H, m), 7.80-7.90 (3H, m), 8.34-8.41 (1H, m), 8.62-8.63 (1H, m)

ESI-MS (m/e): 465 (M+H).

Example 192

1-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxylic acid methyl ester

Using D,L-proline methyl ester hydrochloride, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.83-2.03 (3H, m), 2.20-2.28 (1H, m), 3.05 (3H, s), 3.20-3.86 (2H, m), 3.54 (3H, s), 4.28-4.53 (1H, m), 6.91-7.37 (3H, m), 7.32-7.38 (2H, m), 7.81-7.87 (3H, m), 8.30-8.39 (1H, m), 8.61-8.62 (1H, m).

ESI-MS (m/e): 493 (M+H).

Example 193

1-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxylic acid methyl ester amide

Using DL-proline methyl amide hydrochloride, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.03 (3H, m), 2.25-2.40 (1H, m), 2.46-2.53 (3H, m), 3.06 (3H, s), 3.20-3.26 (1H, m), 3.60-3.78 (1H, m), 4.18-4.24 (1H, m), 7.02-7.60 (3H, m), 7.03 (2H, d, J = 9.0 Hz), 7.82-7.92 (1H, m), 7.89 (2H, d, J = 9.0 Hz), 8.35 (1H, d, J = 7.4 Hz), 8.63 (1H, d, J = 4.7

Hz).

ESI-MS (m/e): 492 (M+H).

Example 194

1-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using DL-proline amide hydrochloride, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.91-2.03 (3H, m), 2.26-2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18-3.28 (1H, m), 3.63-3.91 (1H, m), 4.13-4.29 (1H, m), 6.04-6.33 (1H, m), 6.86-7.28 (4H, m), 7.37-7.41 (1H, m), 7.48-7.54 (1H, m), 7.80-7.92 (3H, m), 8.34-8.38 (1H, m), 8.48-8.63 (1H, m)

ESI-MS (m/e): 478 (M+H).

Example 195

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-piperidine-1-yl)-ethanone

Step 1

Synthesis of 2-(2-(4-fluoro-5-nitro-phenyl)-pyridine

Tetrakis triphenylphosphine palladium 0.55 g was added to 1,4-dioxane 20 ml solution of 2-trimethyl tin-pyridine 2.3 g and 3-bromo-4-fluoro-nitrobenzene 2.1 g and the reaction liquor was heated under reflux overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 7/1), and the title compound was obtained as yellow solid.

Step 2

Synthesis of 2-(2-(4-fluoro-phenoxy)-5-nitro-phenyl)-pyridine

To dimethylformamide 10 ml solution of 4-fluoro-phenol 347 mg and 4-fluoro-3-pyridyl nitrobenzene 600 mg was added potassium carbonate 713 mg, and the reaction liquor was stirred at 100°C for one hour. After cooling, water was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1), and the title compound was obtained as a straw-coloured solid.

Step 3

Synthesis of 4-(4-fluoro-phenoxy-3-pyridine-2-yl-phenyl)-carbamic acid t-butyl ester

10 % palladium-carbon catalyst 100 mg was added to ethyl acetate 10 ml solution of 2-(2-(4-fluoro-phenoxy)-5-nitro-phenyl)-pyridine 840 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To tetrahydrofuran 10 ml solution of the obtained crude product, di-t-butyl dicarbonate 1.5 g was added, and the reaction liquor was stirred at 60°C overnight. The reaction liquor was cooled, and thereafter the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 10/1), and the title compound was obtained as a white solid.

Step 4Synthesis of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-phenyl)-piperidine-1-yl)-ethanone

To ethanol 20 ml solution of 4-(4-fluoro-phenoxy-3-pyridine-2-yl-phenyl)-carbamic acid t-butyl ester 300 mg were added acetic anhydride 0.3 ml and 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the filtrate was eliminated by distillation under reduced pressure, and the crude product was obtained. The obtained crude product was dissolved in 4 N hydrochloric acid-1,4-dioxane 5 ml, and the reaction liquor was stirred at room temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction with ethyl acetate was carried out, and the organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a straw-coloured solid.

Step 5Synthesis of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-4-nitro-phenyl)-piperidine-1-yl)-ethanone

To trifluoroacetic acid 1 ml solution of 190 mg of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-phenyl)-piperidine-1-yl)-ethanone was added potassium nitrate 64 mg, and the reaction liquor was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquor and neutralization caused, and thereafter, it was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained as yellow solid.

Step 6

Production of 1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-piperidine-1-yl)-ethanone

To ethanol 10 ml solution of 180 mg of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-4-nitro-phenyl)-piperidine-1-yl)-ethanone was added expanded Raney nickel catalyst 50 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the filtrate was eliminated by distillation under reduced pressure, and crude product 171 mg was obtained. The obtained crude product 50 mg was dissolved in N-methylpyrrolidone 1 ml, and pyridine-2-carboxaldehyde 16 mg was added, and the reaction liquor was stirred at room temperature for three days. Water was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the reaction mixture was purified using reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the title compound was obtained as a straw-coloured solid.

¹H-NMR (CDCl₃) δ : 1.60-1.85 (3H, m), 1.92-2.09 (5H, m), 2.22-2.30 (1H, m), 3.50-3.78 (2H, m), 5.35-5.38 (1H, m), 6.94-7.08 (5H, m), 7.32-7.38 (2H, m), 7.84-7.89 (1H, m), 8.35-8.38 (1H, m), 8.62-8.67 (1H, m).

ESI-MS (m/e): 431 (M+H).

Example 196

5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Step 1

Synthesis of (3-fluoro-4-hydroxy-phenyl)-carbamic acid tert-butyl ester

To 3-fluoro-4-hydroxy nitrobenzene 6.15 g and methanol 100 ml solution of di-tert-butyl carbonate 930 mg, 10 % palladium-carbon catalyst 600 mg was added, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure, and, by the residue obtained by recovering by filtration with ethyl acetate-hexane mixed solvent, the title compound was obtained.

Step 2

Synthesis of (3-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-phenyl)-carbamic acid tert-butyl ester

To N-methylpyrrolidinone 50 ml solution of (3-fluoro-4-hydroxy-phenyl)-carbamic acid

tert-butyl ester 4.74 g obtained in (Step 1) were added 5-chloro-2-methanesulphonyl-pyridine 4.00 g and cesium carbonate 8.80 g, and the reaction liquor was stirred at 100°C for two hours. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained.

Step 3

Synthesis of 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine

To trifluoroacetic acid 35 ml solution of (3-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-phenyl)-carbamic acid tert-butyl ester 3.38 g obtained in (Step 2) was added potassium nitrate 0.98 g, and the reaction liquor was stirred at room temperature for one hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2), and the title compound was obtained.

Step 4

Synthesis of 5-(2-cyano-phenoxy)-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine

To N-methylpyrrolidinone 2 ml solution of 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine 150 mg obtained in (Step 3) were added potassium carbonate 70 mg and 2-hydroxy-benzonitrile 60 mg, and the reaction liquor was stirred at 90°C for five hours. Water was added to the reaction liquor, and thereafter the title compound was obtained by recovering the precipitate by filtration.

Step 5

Synthesis of 4-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine

To methanol 5 ml solution of 5-(2-cyano-phenoxy)-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine 161 mg obtained in (Step 4) was added expanded Raney nickel catalyst 20 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration and thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

Step 6

Production of 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To methanol 1 ml solution of 4-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 37 mg obtained in (Step 5) were added pyridine-2-carboxaldehyde 0.007 ml and nitrobenzene 0.5 ml, and the reaction liquor was stirred at 120°C overnight. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by silica gel column chromatography (eluent: chloroform / methanol = 20/1) and by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as a brown solid.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 6.94 (1H, d, J = 7.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.41-7.47 (1H, m), 7.47 (1H, t, J = 7.8 Hz), 7.53 (1H, dd, J = 7.8, 2.3 Hz), 7.56-7.61 (1H, m), 7.66 (1H, d, J = 7.8 Hz), 7.72 (1H, s), 7.78 (1H, s), 8.04 (1H, d, J = 7.8 Hz), 8.26 (1H, d, J = 2.3 Hz), 8.35 (1H, d, J = 7.8 Hz), 8.80 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 484 (M+H).

Example 197

5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To dimethylformamide 2 ml solution of 4-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 72 mg obtained in Example 196 (Step 5) were added pyrazine-2-carboxylic acid 21 mg, hydroxybenzotriazole 52 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide · monohydrochloride 52 mg, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was dissolved in N-methylpyrrolidinone 1 ml, and ytterbium tri (trifluoromethane sulfonate) 20 mg was added, and the reaction liquor was stirred at 160°C for two hours. The reaction liquor was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by silica gel column chromatography (eluent: chloroform / methanol = 30/1) and by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a brown solid.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 6.93 (1H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.43 (1H, dd, J = 8.6, 2.3 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.67-7.90 (2H, m), 8.03 (1H, d, J = 8.6 Hz), 8.25 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 2.3 Hz), 8.81 (1H, d, J = 2.3 Hz),

9.53 (1H, s).

ESI-MS (m/e): 485 (M+H).

Example 198

5-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole obtained in Example 196, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.23 (3H, s), 6.85-6.91 (1H, m), 7.17 (1H, t, J = 7.8 Hz), 7.40-7.45 (2H, m), 7.53 (1H, dd, J = 7.8, 4.3 Hz), 7.55-7.78 (1H, m), 7.88 (1H, dd, J = 7.8, 2.3 Hz), 7.99 (1H, d, J = 8.6 Hz), 8.02 (1H, td, J = 7.8, 2.3 Hz), 8.27 (1H, d, J = 2.3 Hz), 8.34 (1H, d, J = 7.8 Hz), 8.78 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 502 (M+H).

Example 199

5-(2-carbamoyl-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole obtained in Example 197, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.22 (3H, s), 6.87-6.91 (1H, m), 7.15-7.22 (1H, m), 7.41-7.46 (2H, m), 7.51-7.85 (2H, m), 7.87 (1H, dd, J = 7.8, 2.3 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.25-8.28 (1H, m), 8.73-8.75 (1H, m), 8.80-8.82 (1H, m), 9.51-9.54 (1H, m).

ESI-MS (m/e): 503 (M+H).

Example 200

5-(2-fluoro-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-fluorophenol, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.20 (3H, s), 6.97-7.04 (1H, m), 7.05-7.15 (3H, m), 7.33 (1/2H, dd, J = 8.8, 2.8 Hz), 7.34 (1/2H, dd, J = 8.8, 2.8 Hz), 7.36-7.42 (1H, m), 7.42 (1/2H, s), 7.70 (1/2H, s),

7.86-7.91 (1H, m), 7.99 (1/2H, d, J = 8.8 Hz), 8.00 (1/2H, d, J = 8.8 Hz), 8.34-8.40 (1H, m), 8.44 (1H, d, J = 2.8 Hz), 8.61-8.65 (1H, m), 10.85 (1/2H, brs), 10.96 (1/2H, brs)
ESI-MS (m/e): 477 (M+H).

Example 2015-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2-fluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 200, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.21 (3H, s), 7.02-7.08 (1H, m), 7.09-7.17 (3H, m), 7.11 (1/2H, s), 7.34 (1/2H, dd, J = 8.6, 2.7 Hz), 7.36 (1/2H, dd, J = 8.6, 2.7 Hz), 7.42 (1/2H, s), 7.43 (1/2H, s), 7.74 (1/2H, s), 8.01 (1/2H, d, J = 8.6 Hz), 8.02 (1/2H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.58 (1/2H, dd, J = 2.7, 1.6 Hz), 8.60 (1/2H, dd, J = 2.7, 1.6 Hz), 8.67 (1/2H, d, J = 2.7 Hz), 8.68 (1/2H, d, J = 2.7 Hz), 9.59 (1/2H, d, J = 1.6 Hz), 9.62 (1/2H, d, J = 1.6 Hz), 10.47 (1/2H, brs), 10.61 (1/2H, brs)

ESI-MS (m/e): 478 (M+H).

Example 2025-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To dimethylformamide 0.5 ml solution of 4-(2-fluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 15 mg obtained in Example 200 was added 1H-pyrazole-3-carboxaldehyde 3.9 mg, and the reaction liquor was stirred at 90°C for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 9/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 3.20 (3H, s), 6.94-6.99 (1H, m), 7.01-7.15 (4H, m), 7.25-7.65 (2H, m), 7.31 (1H, dd, J = 8.9, 2.7 Hz), 7.66 (1H, d, J = 2.3 Hz), 7.98 (1H, d, J = 8.9 Hz), 8.40 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 466 (M+H).

Example 2035-(2-fluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To dimethylformamide 0.5 ml solution of 4-(2-fluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 15 mg obtained in Example 200

were added 1-methyl-1H-pyrazole-3-carboxylic acid 4.3 mg, hydroxybenzotriazole 6.0 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 8.5 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with chloroform and was washed using water, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and p-toluenesulfonic acid 3 mg was added to the obtained residue, and the reaction liquor was stirred at 120°C for two hours. The reaction liquor was diluted with ethyl acetate, and after washing with water, it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 3.19 (3H, s), 3.97 (3H, s), 6.94-7.00 (1H, m), 6.99 (1/2H, brs), 7.00-7.14 (4H, m), 7.27-7.33 (1H, m), 7.30 (1/2H, brs), 7.40 (1/2H, brs), 7.46 (1H, d, J = 2.4 Hz), 7.65 (1/2H, brs), 7.98 (1H, d, J = 8.8 Hz), 8.42 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 480 (M+H).

Example 204

5-(2-chloro-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Step 1

Synthesis of 4-(2-chlorophenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-chlorophenol, the title compound was obtained by the same process as in Example 196 (Step 4)-(Step 5), a process based on these or a combination of these with a normal procedure.

Step 2

Production of 5-(2-chloro-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To methanol 1 ml solution of 4-(2-chlorophenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 35 mg obtained in (Step 1) were added aniline and 1 M methanol solution 0.26 ml of pyridine-2-carboxaldehyde (1 : 1), and the reaction liquor was stirred at 60°C overnight. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous sodium sulphate.

The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a straw-coloured solid.

¹H-NMR(CD₃OD) δ : 3.17 (3H, s), 6.92 (1H, d, J = 8.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.22 (1H, t, J = 8.0 Hz), 7.26-7.66 (4H, m), 7.66-7.80 (1H, brs), 7.90-8.08 (2H, m), 8.29 (1H, d, J = 8.0 Hz), 8.31 (1H, d, J = 2.4 Hz), 8.72 (1H, s).

ESI-MS (m/e): 493 (M+H).

Example 205

5-(2-chloro-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.5 ml solution of 4-(2-chloro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 38 mg obtained in Example 204 (Step 1) were added methylpyrazine-2-imidate (Pyrazine-2-carboximidic acid methyl ester) 15 mg and methanesulfonic acid 0.0065 ml, and the reaction liquor was stirred at 120°C for 20 minutes. The reaction liquor was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. By eliminating the solvent under reduced pressure, the title compound was obtained as yellow colored solid.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 6.97 (1H, d, J = 7.8 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.26 (1H, t, J = 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.48 (1H, dd, J = 8.6, 2.3 Hz), 7.60-7.82 (2H, m), 8.02 (1H, d, J = 8.6 Hz), 8.35 (1H, d, J = 2.3 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 494 (M+H).

Example 206

5-(2-trifluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-trifluoromethyl phenol, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.17 (3H, s), 6.93-6.98 (1H, m), 7.21 (1H, t, J = 7.4 Hz), 7.40-7.81 (6H, m), 7.97-8.05 (2H, m), 8.24-8.39 (2H, m), 8.73-8.87 (1H, m).

ESI-MS (m/e): 527 (M+H).

Example 207

5-(2-trifluoromethyl-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

zimidazole

Using

4-(2-trifluoromethyl-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 206 and methylpyrazine-2-imidate, the title compound was obtained as yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.17 (3H, s), 6.97 (1H, d, J = 7.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.46 (1H, dd, J = 8.6, 2.3 Hz), 7.54 (1H, t, J = 7.8 Hz), 7.44-7.60 (1H, m), 7.65 (1H, d, J = 7.8 Hz), 7.84-7.86 (1H, m), 8.01 (1H, d, J = 8.6 Hz), 8.31 (1H, d, J = 2.3 Hz), 8.73 (1H, d, J = 2.3 Hz), 8.80 (1H, d, J = 2.3 Hz), 9.50 (1H, s)

ESI-MS (m/e): 528 (M+H).

Example 2085-(3-trifluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 3-trifluoromethyl phenol, the title compound was obtained as a white solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 7.00-7.15 (2H, m), 7.37 (1H, d, J = 7.8 Hz), 7.45-7.55 (3H, m), 7.66 (1H, d, J = 10.0 Hz), 7.76 (1H, brs), 7.99-8.04 (2H, m), 8.30-8.35 (2H, m), 8.77 (1H, d, J = 2.7 Hz)

ESI-MS (m/e): 527 (M+H).

Example 2095-(4-trifluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 4-trifluoromethyl phenol, the title compound was obtained as a white solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 6.98 (2H, d, J = 8.6 Hz), 7.46-7.77 (4H, m), 7.60 (2H, d, J = 8.6 Hz), 8.00-8.04 (2H, m), 8.31 (1H, d, J = 3.1 Hz), 8.34 (1H, d, J = 8.2 Hz), 8.78 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 527 (M+H).

Example 2105-(2-difluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

imidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-difluoromethyl phenol, the title compound was obtained as a brown solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.17 (3H, s), 6.70 (1H, t, J = 55.2 Hz), 6.87 (1H, d, J = 7.4 Hz), 7.18 (1H, t, J = 7.4 Hz), 7.40-7.46 (2H, m), 7.50-7.59 (3H, m), 7.59-7.82 (1H, m), 7.98-8.04 (2 H, m), 8.27-8.35 (2H, m), 8.76 (1H, brs)

ESI-MS (m/e): 509 (M+H).

Example 2115-(2-fluoropyridine-3-yloxy)-6-(6-methanesulphonyl
pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-fluoro-pyridin-3-ol synthesised by a process described in Journal of Medicinal Chemistry, 1999, vol. 42, issue 12, pp.2251-2259, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.21 (3H, s), 7.11-7.17 (1H, m), 7.22 (1/2H, s), 7.29-7.36 (2H, m), 7.29-7.36 (1/2H, m), 7.40-7.43 (1H, s), 7.53 (1/2H, s), 7.72 (1/2H, s), 7.88-7.93 (1H, m), 7.93-7.96 (1H, m), 7.99-8.03 (1H, m), 8.37-8.41 (2H, m), 8.65-8.67 (1H, m), 10.78 (1/2H, brs), 10.82 (1/2H, brs).

ESI-MS (m/e): 478 (M+H).

Example 2125-(2-fluoropyridine-3-yloxy)-6-(6-methanesulphonyl pyridine-3-yloxy)-2-pyrazine-2-yl
-1H-benzimidazole

Using 4-(2-fluoro-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene -1,2-diamine obtained in Example 211 and pyrazine-2-carboxylic acid, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.21 (3H, s), 7.14-7.19 (1H, m), 7.23 (1/2H, s), 7.26-7.40 (2H, m), 7.46 (1/2H, s), 7.54 (1/2H, s), 7.56 (1/2H, s), 7.96-8.00 (1H, m), 8.03 (1H, dd, J = 8.6, 3.9 Hz), 8.41 (1H, dd, J = 2.7, 1.6 Hz), 8.62 (1H, ddd, J = 4.7, 2.7, 1.6 Hz), 8.69-8.71 (1H, m), 9.62 (1H, dd, J = 6.3, 1.6 Hz), 10.48 (1/2H, brs), 10.56 (1/2H, brs).

ESI-MS (m/e): 479 (M+H).

Example 213

5-(2-fluoropyridine-3-yloxy)-2-(1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1H-pyrazole-3-carboxaldehyde and 4-(2-fluoro-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 211, the title compound was obtained as a colourless solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.21 (3H, s), 7.08 (1H, d, J = 2.3 Hz), 7.09-7.19 (1H, m), 7.19-7.49 (4H, m), 7.71 (1H, d, J = 2.3 Hz), 7.88-7.96 (1H, m), 7.97-8.03 (1H, m), 8.36 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 467 (M+H).

Example 214

5-(2-fluoropyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-fluoro-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 211, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.20 (3H, s), 4.00 (3H, s), 7.00 (1H, d, J = 2.4 Hz), 7.10-7.16 (1H, m), 7.19 (1/2H, brs), 7.26-7.33 (2H, m), 7.35 (1/2H, brs), 7.48 (1H, d, J = 2.4 Hz), 7.52 (1/2H, brs), 7.67 (1/2H, brs), 7.91-7.94 (1H, m), 8.00 (1H, d, J = 8.6 Hz), 8.37 (1H, d, J = 2.5 Hz), 10.13 (1H, brs).

ESI-MS (m/e): 481 (M+H).

Example 215

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-difluoromethoxy-pyridine-3-ol obtained in Reference Example 2, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 3.22 (3H, s), 7.19-7.27 (1H, m), 7.29-7.86 (6H, m), 7.95-8.07 (3H, m), 8.33-8.35 (1H, m), 8.45-8.48 (1H, m), 8.77 (1H, s).

ESI-MS (m/e): 526 (M+H).

Example 216

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using methylpyrazine-2-imidate and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 215, the title

compound was obtained as a colourless solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 3.20 (3H, s), 7.21 (1H, dd, J = 7-8, 4.9 Hz), 7.30-7.90 (4H, m), 7.62 (1H, t, J = 72.6 Hz), 7.94 (1H, d, J = 8.8 Hz), 7.97 (1H, d, J = 4.8 Hz), 8.45 (1H, d, J = 2.7 Hz), 8.77-8.83 (2H, m), 9.48 (1H, s)

ESI-MS (m/e): 527[M+H].

Example 217

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 215, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 3.22 (3H, s), 4.00 (3H, s), 6.88 (1H, d, J = 2.2 Hz), 7.17-7.82 (6H, m), 7.90-7.99 (3H, m), 8.42-8.45 (1H, m)

ESI-MS (m/e): 529 (M+H).

Example 218

5-(2-cyanopyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Step 1

Synthesis of 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-5-(1-oxy-pyridine-3-yloxy)-phenylamine

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 1-oxy-pyridine-3-ol, the title compound was obtained by the same process as in Example 196 (Step 4), a process based on this or a combination of these with a normal procedure.

Step 2

Synthesis of 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-5-(2-cyano-pyridine-3-yloxy)-phenylamine

To acetonitrile 6 ml solution of 216 mg of 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-5-(1-oxy-pyridine-3-yloxy)-phenylamine were added trimethylsilyl nitrile 0.90 ml and triethylamine 0.90 ml, and thereafter the reaction liquor was stirred while heating under reflux overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, 1,1,1,3,3,3-hexamethyldisilazane was added, and the reaction liquor was stirred while heating under reflux for one hour. The reaction liquor was purified by silica gel column

chromatography (eluent: chloroform/methanol = 30/1), and the title compound was obtained.

Step 3

Production of 5-(2-cyanopyridine-3-yloxy)-6-(6-methanesulphonyl pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-5-(2-cyano-pyridine-3-yloxy)-phenylamine, the title compound was obtained as a white solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.22 (3/2H, s), 3.23 (3/2H, s), 7.18-7.23 (2H, m), 7.40-7.48 (2H, m), 7.50 (1H, s), 7.76-7.78 (1H, m), 7.91-7.95 (1H, m), 8.03-8.06 (1H, m), 8.20-8.23 (1H, m), 8.37-8.44 (2H, m), 8.58-8.67 (1H, m), 11.04 (1H, brs).

ESI-MS (m/e): 485 (M+H).

Example 219

5-(2-cyanopyridine-3-yloxy)-6-(6-methanesulphonyl pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-cyanopyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 218 (Step 3) and pyrazine-2-carboxylic acid, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.23 (3/2H, s), 3.24 (3/2H, s), 7.21-7.26 (2H, m), 7.42-7.48 (1H, m), 7.55 (1H, d, J = 1.2 Hz), 7.80 (1/2H, s), 7.82 (1/2H, s), 8.04 (1/2H, s), 8.06 (1/2H, s), 8.19-8.21 (1H, m), 8.41 (1H, dd, J = 4.5, 1.2 Hz), 8.65 (1H, dd, J = 3.9, 2.3 Hz), 8.73 (1H, d, J = 2.3 Hz), 9.65 (1H, d, J = 1.2 Hz), 10.99 (1H, brs).

ESI-MS (m/e): 486 (M+H).

Example 220

5-(2-cyanopyridine-3-yloxy)-2-(1H-pyrazol-3-yl)-6-(6-methanesulfonyl pyridine-3-yloxy)-1H-benzimidazole

Using 4-(2-cyanopyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 218 (Step 3) and 1H-pyrazole-3-carboxaldehyde, the title compound was obtained as a colourless solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.22 (3H, s), 7.12 (1H, d, J = 2.3 Hz), 7.17-7.25 (2H, m), 7.40-7.48 (2H, m), 7.71-7.74 (1H, m), 7.72 (1H, d, J = 2.3 Hz), 8.00-8.03 (1H, m), 8.17-8.21 (1H, m), 8.38-8.41 (1H, m).

ESI-MS (m/e): 474 (M+H).

Example 2215-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole**Step 1**Synthesis of 3-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-phenylamine

To dimethylformamide 150 ml solution of (3-fluoro-4-hydroxy-phenyl)-carbamic acid tert-butyl ester 10.0 g obtained in Example 196 (Step 1) were added 5-chloro-2-ethane sulfonyl-pyridine 10.9 g and cesium carbonate 21.6 g, and the reaction liquor was stirred at 100°C for three hours. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/9), and crude product was obtained. The obtained crude product was dissolved in 4 N hydrochloric acid-dioxane and was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was diluted with chloroform and was washed using water, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/9), and the title compound was obtained.

Step 2Synthesis of 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine

To 3-fluoro-4-(6-ethane sulfonyl-pyridine-3-yloxy)-phenylamine 10.5 g dissolved in trifluoroacetic acid 100 ml solution was added potassium nitrate 3.8 g, and the reaction liquor was stirred at room temperature for one hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2), and the title compound was obtained.

Step 3Production of 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-ethane sulfonyl-pyridine-3-yloxy)-1H-benzimidazole

To 3 ml solution of N-methylpyrrolidinone of 5-fluoro-4-(6-ethane sulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine 150 mg were added 2-hydroxy-benzonitrile 60 mg and potassium carbonate 70 mg, and the reaction liquor was stirred at 90°C for five hours. Water was added to the reaction liquor, and thereafter, crude product was obtained by recovering the precipitate by

filtration. To methanol 5 ml solution of the obtained crude product, expanded Raney nickel catalyst 10 mg and hydrazine • monohydrate 0.12 ml were added, and the reaction liquor was stirred for one hour. The catalyst was eliminated by filtration, thereafter the solvent was eliminated by distillation under reduced pressure, and crude product 160 mg was obtained. To methanol 3 ml solution of the obtained crude product 35 mg, 1M methanol solution 0.20 ml of aniline and pyridine-2-carboxaldehyde (1 : 1) was added, and the reaction liquor was stirred at 80°C overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as yellow solid.

¹H-NMR(CD₃OD) δ : 1.27 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 6.91 (1H, d, J = 7.8 Hz), 7.19 (1H, t, J = 7.8 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.50-7.60 (2H, m), 7.60-7.90 (3H, m), 7.99-8.04 (2H, m), 8.26 (1H, s), 8.34 (1H, d, J = 7.8 Hz), 8.77 (1H, s).

ESI-MS (m/e): 498 (M+H).

Example 222

5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 4-(2-cyano-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 221 (Step 3) and methylpyrazine-2-imidate, the title compound was obtained as a brown solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.28 (3H, t, J = 7.6 Hz), 3.38 (2H, q, J = 7.6 Hz), 6.94 (1H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.45 (1H, dd, J = 8.6, 2.7 Hz), 7.58 (1H, td, J = 7.6, 1.8 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.68-7.90 (2H, m), 8.03 (1H, d, J = 8.6 Hz), 8.28 (1H, d, J = 2.7 Hz), 8.75 (1H, d, J = 2.0 Hz), 8.82 (1H, dd, J = 2.0, 1.2 Hz), 9.54 (1H, 1.2 Hz = d).

ESI-MS (m/e): 499 (M+H).

Example 223

5-(2-fluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-fluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.18-1.24 (3H, m), 3.02-3.41 (2H, m), 6.97-7.40 (5H, m), 7.47-7.77 (3H, m), 7.96-8.04 (2H, m), 8.30 (1H, d, J = 7.8 Hz), 8.39-8.42 (1H, m), 8.73-8.78 (1H, m).

ESI-MS (m/e): 491 (M+H).

Example 224

5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole
Using 4-(2-fluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 223 and methylpyrazine-2-imidate, the title compound was obtained as a brown solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.22 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 7.52 (1H, dd, J = 3.1, 8.6 Hz), 7.00-7.80 (6H, m), 8.04 (1H, d, J = 8.6 Hz), 8.42 (1H, d, J = 3.1 Hz), 8.72 (1H, s), 8.79 (1H, s), 9.49 (1H, s).

ESI-MS (m/e): 492 (M+H).

Example 225

5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1H-pyrazole-3-carboxaldehyde and 4-(2-fluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 223, the title compound was obtained as a straw-coloured solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.22 (3H, t, J = 7.4 Hz), 3.30-3.42 (2H, m), 6.88 (1H, d, J = 1.6 Hz), 6.99-7.04 (1H, m), 7.07-7.20 (3H, m), 7.22-7.43 (1H, m), 7.49 (1H, dd, J = 7.8, 3.1 Hz), 7.56-7.68 (1H, m), 7.83 (1H, d, J = 1.6 Hz), 8.02 (1H, d, J = 7.8 Hz), 8.39 (1H, d, J = 3.1 Hz).

ESI-MS (m/e): 480 (M+H).

Example 226

5-(2,3-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,3-difluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.69-6.75 (1H, m), 6.91-7.02 (2H, m), 7.20 (1/2H, s), 7.27-7.34 (1H, m), 7.37-7.47 (1H, m), 7.41 (1/2H, s), 7.53 (1/2H, s), 7.72 (1/2H, s), 7.87-7.92 (1H, m), 8.00 (1/2H, d, J = 8.7 Hz), 8.01 (1/2H, d, J = 8.7 Hz), 8.36-8.41 (1H, m), 8.42 (1H, d, J = 2.7 Hz), 8.63-8.67 (1H, m), 10.75 (1/2H, brs), 10.80 (1/2H, brs).

ESI-MS (m/e): 509 (M+H).

Example 227

5-(2,3-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

ole

Using 4-(2,3-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 226 and pyrazine-2-carboxylic acid, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 6.72-6.78 (1H, m), 6.92-7.05 (2H, m), 7.22 (1/2H, s), 7.33 (1/2H, dd, J = 8.8, 2.7 Hz), 7.34 (1/2H, dd, J = 8.8, 2.7 Hz), 7.45 (1/2H, s), 7.53 (1/2H, s), 7.75 (1/2H, s), 8.01 (1/2H, d, J = 8.8 Hz), 8.02 (1/2H, d, J = 8.8 Hz), 8.43 (1H, d, J = 2.7 Hz), 8.60 (1/2H, dd, J = 2.5, 1.6 Hz), 8.62 (1/2H, dd, J = 2.5, 1.6 Hz), 8.69 (1/2H, d, J = 2.5 Hz), 8.70 (1/2H, d, J = 2.5 Hz), 9.61 (1/2H, d, J = 1.6 Hz), 9.63 (1/2H, d, J = 1.6 Hz), 10.52 (1/2H, brs), 10.62 (1/2H, brs).

ESI-MS (m/e): 510 (M+H).

Example 228

5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2,3-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 226, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (1H, q, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.97 (2H, s), 3.98 (1H, s), 6.65-6.75 (1/3H, m), 6.87 (1/2H, brs), 6.89-7.01 (3H, m), 7.10-7.19 (1H, m), 7.26-7.38 (1H, m), 7.30 (1/2H, s), 7.45 (2/3H, d, J = 2.3 Hz), 7.47 (1/3H, d, J = 2.3 Hz), 7.50-7.53 (1/6H, m), 7.62-7.67 (2H, m), 7.95-8.05 (1H, m), 8.39 (1/3H, d, J = 2.5 Hz), 8.54 (2/3H, d, J = 2.5 Hz), 10.00-10.25 (1H, m).

ESI-MS (m/e): 512 (M+H).

Example 229

5-(2,4-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,4-difluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (1H, q, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 6.81-6.95 (2H, m), 6.95-7.05 (1H, m), 7.06 (1/2H, s), 7.33 (1/2H, s), 7.32 (1/2H, dd, J = 8.6, 2.7 Hz), 7.34 (1/2H, dd, J = 8.6, 2.7 Hz), 7.37-7.41 (1H, m), 7.40 (1/2H, s), 7.70 (1/2H, s), 7.86-7.91 (1H, m), 8.00 (1/2H, d, J = 8.6 Hz), 8.01 (1/2H, d, J = 8.6 Hz), 8.34-8.39 (1H, m), 8.46 (1H, d, J

= 2.7 Hz), 8.62-8.67 (1H, m), 10.67 (1/2H, brs), 10.76 (1/2H, brs).

ESI-MS (m/e): 509 (M+H).

Example 230

5-(2,4-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2,4-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 229, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.30 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 6.82-6.95 (2H, m), 6.98-7.05 (1H, m), 7.08 (1/2H, s), 7.34 (1/2H, dd, J = 8.6, 2.7 Hz), 7.35 (1/2H, dd, J = 8.6, 2.7 Hz), 7.38 (1/2H, s), 7.44 (1/2H, s), 7.74 (1/2H, s), 8.02 (1/2H, d, J = 8.6 Hz), 8.03 (1/2H, d, J = 8.6 Hz), 8.46 (1/2H, d, J = 2.7 Hz), 8.47 (1/2H, d, J = 2.7 Hz), 8.58 (1/2H, dd, J = 2.7, 1.6 Hz), 8.60 (1/2H, dd, J = 2.7, 1.6 Hz), 8.67 (1/2H, d, J = 2.7 Hz), 8.68 (1/2H, d, J = 2.7 Hz), 9.59 (1/2H, d, J = 1.6 Hz), 9.61 (1/2H, d, J = 1.6 Hz), 10.54 (1/2H, brs), 10.69 (1/2H, brs).

ESI-MS (m/e): 510 (M+H).

Example 231

5-(2,4-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2,4-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 229, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.28 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 3.98 (3H, s), 6.78-6.85 (1H, m), 6.85-6.93 (1H, m), 6.93-6.98 (1H, m), 6.93-6.98 (1/2H, m), 6.99 (1H, d, J = 2.3 Hz), 7.02 (1/2H, brs), 7.27-7.34 (1H, m), 7.36 (1/2H, brs), 7.46 (1H, d, J = 2.3 Hz), 7.64 (1/2H, brs), 7.99 (1H, d, J = 8.6 Hz), 8.43 (1H, d, J = 2.7 Hz), 10.19 (1/2H, brs), 10.29 (1/2H, brs).

ESI-MS (m/e): 512 (M+H).

Example 232

5-(2,5-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,5-difluoro-phenol, the title compound was obtained as a white solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.23 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.76-6.89 (2H, m), 7.15-7.24 (1H, m), 7.49-7.55 (3H, m), 7.71 (1H, s), 8.01 (1H, td, J = 7.4, 2.3 Hz), 8.04 (1H, d, J = 7.4 Hz), 8.32 (1H, d, J = 7.4 Hz), 8.40 (1H, d, J = 2.3 Hz), 8.77 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 509 (M+H).

Example 233

5-(2,5-difluoro-phenoxy)-2-pyridine-1-oxide-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

To chloroform 1.5 ml solution of 5-(2,5-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole 7.5 mg obtained in Example 232 was added m-chloroperbenzoic acid 7.5 mg, and thereafter the reaction liquor was stirred at 45°C for one hour. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a straw-coloured solid.

¹H-NMR(CD₃OD) δ : 1.23 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.78-6.90 (2H, m), 7.20 (1H, td, J = 9.8, 5.1 Hz), 7.52 (1H, dd, J = 6.6, 3.1 Hz), 7.56 (1H, s), 7.62 (1H, t, J = 8.2 Hz), 7.73 (1H, t, J = 8.2 Hz), 7.78 (1H, s), 8.04 (1H, d, J = 8.2 Hz), 8.41 (1H, d, J = 3.1 Hz), 8.51 (1H, d, J = 6.6 Hz), 8.64 (1H, d, J = 8.2 Hz).

ESI-MS (m/e): 525 (M+H).

Example 234

5-(2,5-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using methylpyrazine-2-imidate and 4-(2,5-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 232, the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 6.9 Hz), 3.38 (2H, q, J = 6.9 Hz), 6.77-6.91 (2H, m), 7.17-7.24 (1H, m), 7.51 (1H, s), 7.52 (1H, dd, J = 7.4, 4.3 Hz), 7.74 (1H, s), 8.04 (1H, d, J = 7.4 Hz), 8.41 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 4.3 Hz), 8.80 (1H, dd, J = 2.3, 1.8 Hz), 9.51 (1H, d, J = 1.8 Hz).

ESI-MS (m/e): 510 (M+H).

Example 235

5-(2,6-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,6-difluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 6.68-6.75 (1/2H, m), 6.90-7.00 (2H, m), 7.12-7.26 (1H, m), 7.27-7.53 (3H, m), 7.68-7.72 (1/2H, m), 7.84-7.92 (1H, m), 7.98-8.04 (1H, m), 8.31-8.39 (1H, m), 8.41 (1/2H, d, J = 2.3 Hz), 8.56 (1/2H, d, J = 2.3 Hz), 8.57-8.63 (1H, m), 10.59-10.88 (1H, m).

ESI-MS (m/e): 509 (M+H).

Example 236

5-(2,6-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2,6-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 235, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (1/2H, q, J = 7.4 Hz), 3.39, (1H, q, J = 7.4 Hz), 3.40 (1/2H, q, J = 7.4 Hz), 6.73-6.78 (1/2H, m), 6.93-7.04 (2H, m), 6.93-7.04 (1/2H, m), 7.14-7.20 (1/2H, m), 7.22 (1/4H, s), 7.31-7.42 (1H, m), 7.44 (1/4H, s), 7.45 (1/4H, s), 7.53 (1/4H, s), 7.74 (1/4H, s), 7.75 (1/4H, s), 8.00-8.05 (1H, m), 8.43 (1/2H, d, J = 2.7 Hz), 8.56 (1/4H, dd, J = 2.5, 1.6 Hz), 8.57 (1/2H, d, J = 2.7 Hz), 8.59 (1/4H, dd, J = 2.5, 1.6 Hz), 8.60 (1/4H, dd, J = 2.5, 1.6 Hz), 8.61 (1/4H, dd, J = 2.5, 1.6 Hz), 8.66 (1/4H, d, J = 2.5 Hz), 8.67 (1/4H, d, J = 2.5 Hz), 8.68 (1/4H, d, J = 2.5 Hz), 8.69 (1/4H, d, J = 2.5 Hz), 9.56 (1/4H, d, J = 1.6 Hz), 9.60 (1/4H, d, J = 1.6 Hz), 9.61 (1/4H, d, J = 1.6 Hz), 9.63 (1/4H, d, J = 1.6 Hz), 10.36 (1/4H, brs), 10.48 (1/4H, brs), 10.51 (1/4H, brs), 10.57 (1/4H, brs)

ESI-MS (m/e): 510 (M+H).

Example 237

5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2,6-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 235, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 3.96 (3H, s), 6.87 (1/2H, brs), 6.93-7.00 (3H, m), 7.10-7.17 (1H, m), 7.18 (1/2H, s), 7.30 (1/2H, s), 7.32-7.40 (1H, m), 7.34 (1H, d, J = 2.5 Hz), 7.63 (1/2H, brs), 7.98-8.03 (1H, m), 8.54 (1H, d, J = 2.7 Hz), 10.18 (1/2H, brs), 10.35 (1/2H, brs).

ESI-MS (m/e): 512 (M+H).

Example 238

5-(2-trifluoromethoxy-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-trifluoromethoxy-phenol, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4), (Step 5) and Example 205, a process based on these or a combination of these successively with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.27 (3H, t, J = 7.4 Hz), 3.36 and 3.37 (total 2H, each q, J = 7.4 Hz), 6.95-7.00 (1H, m), 7.12-7.46 (5H, m), 7.50 and 7.76 (total 1H, each s), 7.98 and 8.00 (total 1H, each d, J = 8.8 Hz), 8.41 (1H, d, J = 2.7 Hz), 8.59-8.62 (1H, m), 8.68 (1H, d, J = 2.4 Hz), 9.61 and 9.63 (total 1H, each d, J = 1.6 Hz).

ESI-MS (m/e): 558 (M+H).

Example 239

5-(2-fluoropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-fluoro-pyridin-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 7.11-7.16 (1H, m), 7.24 (1/2H, s), 7.26-7.35 (2H, m), 7.41-7.45 (1H, m), 7.43 (1/2H, s), 7.55 (1/2H, s), 7.72 (1/2H, s), 7.88-7.94 (2H, m), 7.99-8.03 (1H, m), 8.38-8.41 (2H, m), 8.65-8.67 (1H, m), 10.94 (1/2H, brs), 10.98 (1/2H, brs)

ESI-MS (m/e): 492 (M+H).

Example 240

5-(2-fluoropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2-fluoropyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 239, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a

combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.30 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 7.13-7.24 (1H, m), 7.24 (1/2H, s), 7.26-7.39 (2H, m), 7.47 (1/2H, s), 7.56 (1/2H, s), 7.77 (1/2H, s), 7.95-8.05 (2H, m), 8.40 (1H, d, J = 2.3 Hz), 7.62 (1/2H, dd, J = 2.4, 1.6 Hz), 8.63 (1/2H, dd, J = 2.4, 1.6 Hz), 8.70 (1/2H, d, J = 2.4 Hz), 8.71 (1/2H, d, J = 2.4 Hz), 9.62 (1/2H, d, J = 1.6 Hz), 9.63 (1/2H, d, J = 1.6 Hz), 10.45 (1/2H, brs), 10.51 (1/2H, brs).

ESI-MS (m/e): 493 (M+H).

Example 241

5-(2-fluoropyridine-3-yloxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1H-pyrazole-3-carboxaldehyde and 4-(2-fluoropyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 239, the title compound was obtained as a colourless solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.07 (1H, d, J = 2.7 Hz), 7.08-7.13 (1H, m), 7.20 (1/2H, brs), 7.24-7.30 (2H, m), 7.34 (1/2H, brs), 7.52 (1/2H, brs), 7.65 (1/2H, brs), 7.71 (1H, d, J = 2.7 Hz), 7.88-7.92 (1H, m), 7.99 (1H, d, J = 8.6 Hz), 8.33 (1H, d, J = 2.7 Hz)

ESI-MS (m/e): 481 (M+H).

Example 242

5-(2-chloropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2- pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-chloro-pyridin-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 7.14-7.20 (2H, m), 7.28 (1/2H, s), 7.20-7.31 (1H, m), 7.40-7.46 (1H, m), 7.46 (1/2H, s), 7.60 (1/2H, s), 7.76 (1/2H, s), 7.88-7.93 (1H, m), 8.00 (1/2H, d, J = 8.6 Hz), 8.01 (1/2H, d, J = 8.6 Hz), 8.11-8.16 (1H, m), 8.31-8.35 (1H, m), 8.38-8.42 (1H, m), 8.64-8.68 (1H, m), 10.82-10.95 (1H, m).

ESI-MS (m/e): 508 (M+H).

Example 243

5-(2-chloropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2-chloropyridine-3-yloxy)-5-(6-ethane

sulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 242, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.18-7.24 (2H, m), 7.30 (1/2H, s), 7.31 (1/2H, dd, J = 8.6, 2.7 Hz), 7.32 (1/2H, dd, J = 8.6, 2.7 Hz), 7.51 (1/2H, s), 7.61 (1/2H, s), 7.81 (1/2H, s), 8.02 (1/2H, d, J = 8.6 Hz), 8.04 (1/2H, d, J = 8.6 Hz), 8.15-8.20 (1H, m), 8.35 (1/2H, d, J = 2.7 Hz), 8.36 (1/2H, d, J = 2.7 Hz), 8.63 (1/2H, dd, J = 2.3, 1.6 Hz), 8.64 (1/2H, dd, J = 2.3, 1.6 Hz), 8.72 (1/2H, d, J = 2.3 Hz), 8.73 (1/2H, d, J = 2.3 Hz), 9.64 (1/2H, d, J = 1.6 Hz), 9.65 (1/2H, d, J = 1.6 Hz), 10.60 (1/2H, brs), 10.68 (1/2H, brs).

ESI-MS (m/e): 509 (M+H).

Example 244

5-(2-chloropyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-chloropyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 242, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 4.01 (3H, s), 7.01 (1H, d, J = 2.3 Hz), 7.12-7.17 (2H, m), 7.26 (1H, dd, J = 8.8, 2.7 Hz), 7.39 (1/2H, brs), 7.48 (1/2H, brs), 7.49 (1H, d, J = 2.3 Hz), 7.58 (1/2H, brs), 7.69 (1/2H, brs), 7.99 (1H, d, J = 8.8 Hz), 8.10-8.15 (1H, m), 8.31 (1H, d, J = 2.7 Hz), 10.28 (1H, brs).

ESI-MS (m/e): 511 (M+H).

Example 245

5-(2-cyanopyridine-3-yloxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 1-oxy-pyridin-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 218, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.30 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.12-7.26 (3H, m), 7.38-7.45 (2H, m), 7.45 (1/2H, s), 7.46 (1/2H, s), 7.75 (1H, s), 7.89-7.94 (1H, m), 7.99-8.05 (1H, m), 8.22-8.26 (1H, m), 8.39-8.43 (1H, m), 8.67-8.70 (1H, m), 10.88 (1H, brs).

ESI-MS (m/e): 499 (M+H).

Example 246

5-(2-cyanopyridine-3-yloxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyrazine-

2-yl-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2-cyanopyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 245, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.35 (3/2H, t, J = 7.4 Hz), 1.37 (3/2H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 7.19-7.26 (2H, m), 7.42-7.47 (1H, m), 7.53 (1/2H, s), 7.54 (1/2H, s), 7.80 (1/2H, s), 7.81 (1/2H, s), 8.04 (1/2H, d, J = 8.6 Hz), 8.05 (1/2H, d, J = 8.6 Hz), 8.22-8.25 (1H, m), 8.40-8.43 (1H, m), 8.64-8.66 (1H, m), 8.73 (1H, d, J = 2.5 Hz), 9.65 (1H, d, J = 1.5 Hz), 10.87 (1/2H, brs), 10.90 (1/2H, brs)

ESI-MS (m/e): 500 (M-H).

Example 2475-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-difluoromethoxy-pyridin-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 1.10 (3H, t, J = 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 7.18-7.25 (1H, m), 7.31-7.87 (6H, m), 7.94-8.07 (3H, Lm), 8.32-8.36 (1H, m), 8.46-8.49 (1H, m), 8.77 (1H, s).

ESI-MS (m/e): 540 (M+H).

Example 2485-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using methylpyrazine-2-imidate and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 247, the title compound was obtained as a colourless solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.30 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.07-7.11 (1H, m), 7.17 and 7.76 (total 1H, each s), 7.29-7.34 (2H, m), 7.37 (1H, t, J = 72.8 Hz), 7.46 (1H, s), 7.96-8.03 (2H, m), 8.43 (1H, s), 8.60 and 8.62 (total 1H, each s), 8.69 (1H, s), 9.60 and 9.63 (total 1H, each d, J = 1.5 Hz).

ESI-MS (m/e): 541 (M+H).

Example 2495-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-ethane

sulfonyl-pyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 247, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 1.10 (3H, t, J = 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 4.00 (3H, s), 6.88 (1H, d, J = 2.3 Hz), 7.19 (1H, brs), 7.26-7.75 (4H, m), 7.63 (1H, t, J = 72.4 Hz), 7.90-7.99 (3H, m), 8.45 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 543 (M+H).

Example 2506-benzyloxy-5-(2-fluorophenoxy)-2-pyrazine-2-yl-1H-benzimidazole**Step 1**Synthesis of 4-benzyloxy-3-fluoroaniline

To methanol 60 ml solution of 4-benzyloxy-3-fluoro nitrobenzene 4.94 g, 2.91 ml hydrazine monohydrate and about 1 g expanded Raney nickel catalyst were added, and the reaction liquor was stirred at room temperature for two hours. By eliminating the solvent under reduced pressure after eliminating the catalyst by filtration with celite, the title compound was obtained as a yellow oily substance.

Step 2Synthesis of N-(4-benzyloxy-3-fluorophenyl) pyrazine carboxamide

To pyridine 60 ml solution of 4-benzyloxy-3-fluoroaniline 4.13 g, pyrazine-2-carboxylic acid 2.59 g and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 4.73 g were added, and the reaction liquor was stirred at room temperature overnight. Pyridine was eliminated by distillation under reduced pressure, and thereafter, water was added. By recovering the formed precipitate by filtration, the title compound was obtained as a brown solid.

Step 3Synthesis of N-(4-benzyloxy-5-fluoro-2-nitrophenyl) pyrazine carboxamide

To chloroform 40 ml suspension of N-(4-benzyloxy-3-fluorophenyl) pyrazine carboxamide 5.80 g, trifluoroacetic acid 40 ml and potassium nitrate 1.99 g were added under ice cooling, and the reaction liquor was stirred at room temperature overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, saturated aqueous sodium bicarbonate was added. The formed precipitate was recovered by filtration and thereafter, washed using water. By washing the obtained solid with mixed solvent of ethyl acetate and hexane, the title compound was obtained as yellow solid.

Step 4Synthesis of N-(4-benzyloxy-5-(2-fluorophenoxy)-2-nitrophenyl) pyrazine carboxamide

To dimethylformamide 16 ml solution of N-(4-benzyloxy-5-fluoro-2-nitrophenyl) pyrazine carboxamide 2.14 g, 2-fluorophenol 0.54 ml and potassium carbonate 2.53 g were added, and the reaction liquor was stirred at 90°C for five hours, and thereafter, water was added. By recovering the formed precipitate by filtration, the title compound was obtained as yellow solid.

Step 5Production of 5-benzyloxy-6-(2-fluorophenoxy)-2-pyrazine-2-yl-1H-benzimidazole

To dimethylformamide 16 ml suspension of N-(4-benzyloxy-5-(2-fluorophenoxy)-2-nitrophenyl) pyrazine carboxamide 1.52 g, tin chloride (II) dihydrate 3.72 g was added, and the reaction liquor was stirred at 80°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and, by washing the obtained residue with mixed solvent of ethyl acetate and hexane, the title compound was obtained as yellow solid.

¹H-NMR (DMSO-d₆) δ : 5.15 and 5.17 (total 2H, each s), 6.78-6.93 (1H, m), 7.06-7.40 (9H, m), 7.54 and 7.57 (total 1H, each s), 8.73 and 8.74 (total 1H, each s), 8.76-8.79 (1H, m), 9.43 and 9.44 (total 1H, each d, J = 1.6 Hz).

ESI-MS (m/e): 413 (M+H).

Example 2515-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(2-cyano-pyrimidine-5-yloxy)-1H-benzimidazole**Step 1**Synthesis of 5-(2-fluorophenoxy)-6-hydroxy-2-pyrazine-2-yl-1H-benzimidazole

To tetrahydrofuran 10 ml and methanol 10 ml suspension of 5-benzyloxy-6-(2-fluorophenoxy)-2-pyrazine-2-yl-1H-benzimidazole 697 mg obtained in Example 250 was added 20 % palladium hydroxide-carbon catalyst 500 mg, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for one hour. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: ethyl acetate), and the title compound was obtained as yellow solid.

Step 2Production of 5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(2-cyano-pyrimidine-5-yloxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.5 ml solution of 5-(2-fluorophenoxy)-6-

-hydroxy-2-pyrazine-2-yl-1H-benzimidazole 7.0 mg obtained in Step 1 were added 5-bromo-2-cyano-pyrimidine 7.0 mg and cesium carbonate 15 mg, and thereafter the reaction liquor was stirred at 90°C for 15 minutes. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. By eliminating the solvent under reduced pressure, the title compound was obtained as a colourless solid.

¹H-NMR(CD₃OD) δ : 7.01-7.58 (5H, m), 7.64-7.82 (1H, m), 8.52 (2H, s), 8.67 (1H, s), 8.74 (1H, s), 9.44 (1H, s).

ESI-MS (m/e): 426 (M+H).

Example 252

5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-cyano-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(2-fluorophenoxy)-6-hydroxy-2-pyrazine-2-yl-1H-benzimidazole obtained in Example 251 (Step 1) and 5-bromo-2-cyanopyridine, the title compound was obtained as yellow solid by the same process as in Example 251 (Step 2), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 7.01-7.30 (5H, m), 7.42 (1H, dd, J = 8.6, 3.1 Hz), 7.55-7.77 (1H, m), 7.81 (1H, d, J = 8.6 Hz), 8.39 (1H, d, J = 3.1 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.47 (1H, s).

ESI-MS (m/e): 425 (M+H).

Example 253

5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-trifluoromethyl-pyridine-3-yloxy)-1H-benzimidazole

To N-methylpyrrolidinone 1 ml solution of 21 mg of 5-(2-fluorophenoxy)-6-hydroxy-2-pyrazine-2-yl-1H-benzimidazole obtained in Example 251 (Step 1) were added 5-bromo-2-trifluoromethyl-pyridine 16 mg, cesium carbonate 50 mg and copper (II) oxide 10 mg, and thereafter the reaction liquor was stirred at 130°C for five hours. The precipitate was separated by filtration, and thereafter the solution was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. By eliminating the solvent under reduced pressure, the title compound was obtained as a brown solid.

¹H-NMR(CD₃OD) δ : 6.70-7.84 (6H, m), 7.49 (1H, dd, J = 8.8 Hz, 2.8 Hz), 7.78 (1H, d, J = 8.8 Hz), 8.39 (1H, d, J = 2.8 Hz), 8.73 (1H, s), 8.80 (1H, s), 9.49 (1H, s).

ESI-MS (m/e): 468 (M+H).

Example 2545-(2,6-difluoro-phenoxy)-4-fluoro-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole**Step 1**Synthesis of 2,3-difluoro-1-(6-methanesulphonyl-pyridine-3-yloxy)-4-nitro-benzene

To 3 ml N-methylpyrrolidinone solution of 2,3,4-trifluoro-nitrobenzene 135 mg were added 6-methanesulphonyl-pyridin-3-ol 112 mg and potassium carbonate 100 mg, and the reaction liquor was stirred at 50°C for one hour. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained.

Step 2Synthesis of N-(2,3-difluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-6-nitro-phenyl) pyrazine carboxamide

To methanol 3 ml solution of 2,3-difluoro-1-(6-methanesulphonyl-pyridine-3-yloxy)-4-nitro-benzene 22 mg were added 0.2 ml hydrazine monohydrate and about 0.01 g expanded Raney nickel catalysts, and the reaction liquor was stirred at room temperature for 15 minutes. The catalyst was eliminated by filtration by celite, and, by eliminating the solvent under reduced pressure, crude product was obtained. To pyridine 1 ml solution of the obtained crude product, pyrazine-2-carboxylic acid 12 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 25 mg were added, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To trifluoroacetic acid 2 ml solution of crude product, fuming nitric acid 0.1 ml was added, and the reaction liquor was stirred at 45°C overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 20/1), and obtained the title compound.

Step 3Production of 5-(2,6-difluoro-phenoxy)-4-fluoro-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To 0.5 ml N-methylpyrrolidinone solution of N-(2,3-difluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-6-nitro-phenyl) pyrazine carboxamide 8.6 mg were added 2,6-difluoro phenol 8 mg and potassium carbonate 8 mg, and the reaction liquor was stirred at

90°C for ten minutes, and thereafter, tin chloride (II) dihydrate 75 mg was added, and the reaction liquor was stirred at 90°C overnight. P-toluenesulfonic acid 3 mg was added furthermore, and the reaction liquor was stirred at 90°C for two hours. The precipitate was eliminated by filtration, and thereafter the solution was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a brown solid.

¹H-NMR(CD₃OD) δ : 3.22 (3H, s), 6.93-6.99 (2H, m), 7.01-7.10 (1H, m), 7.30-7.45 (1H, m), 7.47-7.51 (1H, m), 8.02 (1H, d, J = 8.6 Hz), 8.37 (1H, d, J = 2.3 Hz), 8.75 (1H, d, J = 2.3 Hz), 8.80 (1H, s), 9.56 (1H, s).

ESI-MS (m/e): 514 (M+H).

Example 255

5-(2,6-difluoro-phenoxy)-7-fluoro-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Step 1

Synthesis of 2,3-difluoro-1-(2,6-difluoro-phenoxy)-4-nitro-benzene

To 13 ml N-methylpyrrolidinone solution of 2,3,4-trifluoro-nitrobenzene 500 mg were added 2,6-difluoro-phenol 470 mg and tetrabutylammonium bromide 1.5 g, and the reaction liquor was stirred at 130°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 4/1), and the title compound was obtained.

Step 2

Production of 5-(2,6-difluoro-phenoxy)-7-fluoro-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

2,3-difluoro-1-(2,6-difluoro-phenoxy)-4-nitro-benzene and 6-ethane sulfonyl-pyridin-3-ol obtained in Reference Example 4 were successively used, and, by the same process as in Example 254 (Step 2) and (Step 3), a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.91-6.96 (1H, m), 7.14 (2H, t, J = 8.4 Hz), 7.27-7.34 (1H, m), 7.48-7.54 (1H, m), 7.63 (1H, dd, J = 8.8, 2.7 Hz), 7.99 (1H, t, J = 7.6 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.31-8.37 (1H, m), 8.59 (1H, d, J = 2.7 Hz), 8.70-8.76 (1H, m).

ESI-MS (m/e): 527 (M+H).

Example 256**5-(pyridine-2-yloxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole**

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 2-hydroxypyridine, the title compound was obtained as a brown solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.09 (3H, s), 6.81 (1H, d, J = 8.2 Hz), 7.02 (2H, d, J = 8.6 Hz), 7.02-7.07 (1H, m), 7.49-7.54 (1H, m), 7.55 (1H, s), 7.63 (1H, s), 7.71-7.77 (1H, m), 7.83 (2H, d, J = 8.6 Hz), 7.98-8.03 (2H, m), 8.31 (1H, d, J = 7.6 Hz), 8.76 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 459 (M+H).

Example 257**5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole**

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 2-difluoromethoxy-pyridin-3-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.10 (3H, s), 7.05 (2H, d, J = 8.4 Hz), 7.13-7.20 (1H, m), 7.33-7.70 (4H, m), 7.48 (1H, t, J = 72.8 Hz), 7.87 (2H, d, J = 8.4 Hz), 7.92 (1H, d, J = 4.5 Hz), 8.01 (1H, t, J = 7.4 Hz), 8.32 (1H, d, J = 7.8 Hz), 8.77 (1H, brs).

ESI-MS (m/e): 525 (M+H).

Example 258**5-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole**

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 1-methyl-2-oxo-1,2-dihydro-pyridin-3-ol, the title compound was obtained as a brown solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 3.04 (3H, s), 3.56 (3H, s), 6.06 (1H, td, J = 7.0, 2.7 Hz), 6.84 (1/2H, d, J = 7.4 Hz), 6.88 (1/2H, dd, J = 7.4, 1.8 Hz), 7.05-7.15 (3H, m), 7.20 (1/2H, s), 7.28 (1/2H, d, J = 1.2 Hz), 7.38 (1H, dd, J = 6.6, 4.7 Hz), 7.46 (1/2H, s), 7.60 (1/2H, s), 7.80-7.90 (3H, m), 8.36 (1H, t, J = 7.2 Hz), 8.62 (1H, d, J = 4.4 Hz).

ESI-MS (m/e): 489 (M+H).

Example 259

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole**Step 1**Synthesis of 5-fluoro-4-(4-ethane sulfonyl-phenoxy)-2-nitro-phenylamine

Using 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

Step 2Production of 5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(4-ethanesulfonyl-phenoxy)-2-nitro-phenylamine and 2-difluoromethoxy-pyridin-3-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.20 (3H, t, J = 7.4 Hz), 3.15 (2H, q, J = 7.4 Hz), 7.04 (2H, d, J = 8.4 Hz), 7.06-7.15 (1H, m), 7.30-7.70 (4H, m), 7.46 (1H, t, J = 72.9 Hz), 7.80 (2H, d, J = 8.4 Hz), 7.89 (1H, d, J = 4.3 Hz), 7.99 (1H, t, J = 7.7 Hz), 8.30 (1H, d, J = 8.0 Hz), 8.74 (1H, brs)

ESI-MS (m/e): 539 (M+H).

Example 2605-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 259 (Step 2), the title compound was obtained as a straw-coloured solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.27 and 1.28 (total 3H, each t, J = 7.4 Hz), 3.09 and 3.10 (total 2H, each q, J = 7.4 Hz), 6.98 and 6.99 (total 2H, each d, J = 9.0 Hz), 7.04-7.10 (1H, m), 7.23 and 7.42 (total 1H, each s), 7.25-7.30 (1H, m), 7.36 and 7.37 (total 1H, each t, J = 73.0 Hz), 7.52 and 7.73 (total 1H, each s), 7.80 and 7.81 (total 2H, each d, J = 9.0 Hz), 7.90-7.96 (1H, m), 8.58-8.63 (1H, m), 8.68 and 8.69 (total 1H, each d, J = 2.4 Hz), 9.61 and 9.63 (total 1H, each d, J = 1.5 Hz).

ESI-MS (m/e): 540 (M+H).

Example 2615-(2,4-difluoro-phenoxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-fluoro-5-(4-ethanesulfonyl-phenoxy)-2-nitro-phenylamine obtained in Example 259 (Step 1) and 2,4-difluoro-phenol, the title compound was obtained as a white solid by the same process as in Example 259, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.21 (3H, t, J = 7.4 Hz), 3.19 (2H, q, J = 7.4 Hz), 6.89-6.95 (1H, m), 7.01-7.12 (2H, m), 7.11 (2H, d, J = 8.4 Hz), 7.23-7.67 (3H, m), 7.84 (2H, d, J = 8.4 Hz), 7.99 (1H, t, J = 7.4 Hz), 8.29 (1H, d, J = 8.2 Hz), 8.75 (1H, brs)

ESI-MS (m/e): 508 (M+H).

Example 262

4-(1-methyl-1H-imidazol-2-yl sulphanyl)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

1-methyl-1H-imidazole-2-thiol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

¹H-NMR (CDCl₃) δ : 3.09 (6H, s), 3.87 (3H, s), 6.69 (1H, s), 6.74 (1H, s), 6.79-6.89 (2H, m), 7.07 (2H, d, J = 8.4 Hz), 7.16 (1H, d, J = 2.0 Hz), 7.42 (2H, d, J = 8.4 Hz), 7.53 (1H, t, J = 7.6 Hz), 7.64 (1H, d, J = 2.0 Hz), 8.17 (1H, d, J = 7.4 Hz).

ESI-MS (m/e): 471 (M+H).

Example 263

4-(pyridin-2-yl sulphanyl)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Pyridine-2-thiol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

¹H-NMR (CDCl₃) δ : 3.05 (3H, s), 3.09 (3H, s), 6.90-7.08 (4H, m), 7.30-7.65 (6H, m), 7.85 (1H, t, J = 7.5 Hz), 8.37 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 3.9 Hz), 8.62 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 468 (M+H).

Example 264

4-(2,6-difluoro-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 4-methanesulphonyl-phenol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 3.22 (3H, s), 6.25 (1H, s), 7.16-7.24 (3H, m), 7.49-7.54 (1H, m), 7.60-7.66 (1H, m), 7.70-7.78 (1H, m), 7.95 (2H, d, J = 8.4 Hz), 8.02 (1H, m), 8.40 (1H, d, J = 4.7 Hz), 8.70 (1H, d, J = 2.3 Hz), 8.78 (1H, d, J = 2.3 Hz).

ESI-MS (m/e): 494 (M+H).

Example 265

4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-methanesulphonyl-phenol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a straw-coloured solid.

¹H-NMR(CD₃OD) δ : 3.10 (3H, s), 3.63 (3H, s), 6.35 (1H, t, J = 7.1 Hz), 6.39 (1H, s), 7.06 (1H, s), 7.16 (2H, d, J = 8.0 Hz), 7.34 (1H, d, J = 7.2 Hz), 7.42-7.52 (1H, m), 7.53 (1H, dd, J = 6.8, 1.6 Hz), 7.90 (2H, d, J = 8.0 Hz), 7.91-8.00 (1H, m), 8.28-8.38 (1H, m), 8.71 (1H, s).

ESI-MS (m/e): 489 (M+H).

Example 266

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 6-methanesulphonyl-pyridin-3-ol obtained in Reference Example 3 were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 3.22 (3H, s), 6.39 (1H, s), 7.16-7.24 (2H, m), 7.21 (1H, d, J = 8.6 Hz), 7.32-7.40 (1H, m), 7.54-7.58 (1H, m), 8.06 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.3 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79 (1H, s), 9.56 (1H, s).

ESI-MS (m/e): 496 (M+H).

Example 267

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 266, the title compound was obtained by the same process as in Example 196 (Step 6), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.32 (3H, s), 6.47 (1H, s), 7.19-7.26 (3H, m), 7.34-7.42 (1H, m), 7.56-7.63 (2H, m), 8.05-8.11 (2H, m), 8.41 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.3 Hz), 8.83 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 495 (M+H).

Example 268

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 6-ethanesulfonyl-pyridin-3-ol obtained in Reference Example 4 were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.38 (1H, s), 7.10-7.25 (3H, m), 7.32-7.40 (1H, m), 7.56 (1H, dd, J = 8.6, 2.3 Hz), 8.06 (1H, d, J = 9.0 Hz), 8.48 (1H, d, J

= 2.7 Hz), 8.72 (1H, d, J = 2.7 Hz), 8.79 (1H, s), 9.56 (1H, s).

ESI-MS (m/e): 510 (M+H).

Example 269

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 268, the title compound was obtained by the same process as in Example 196 (Step 6), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.44 (1H, s), 7.18-7.25 (3H, m), 7.32-7.41 (1H, m), 7.55-7.62 (2H, m), 8.03-8.09 (2H, m), 8.41 (1H, d, J = 7.8 Hz), 8.49 (1H, d, J = 2.3 Hz), 8.81 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 509 (M+H).

Example 270

4-(2-fluoro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

2-fluoro-pyridin-3-ol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ : 3.23 (3H, s), 6.09 (1H, d, J = 2.3 Hz), 6.35 (1H, d, J = 2.3 Hz), 7.28 (1H, dd, J = 7.8, 5.5 Hz), 7.59-7.61 (1H, m), 7.66-7.67 (1H, m), 7.84-7.85 (1H, m), 8.6 (1H, d, J = 8.6 Hz), 8.70-8.74 (1H, m), 8.87 (1H, d, J = 2.3 Hz), 9.15 (1H, d, J = 1.6 Hz), 9.86 (1H, s).

ESI-MS (m/e): 479 (M+H).

Examples 271, 272

4-(2-fluoro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole and

4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

2-fluoro-pyridin-3-ol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Examples 108-1 and 108-2, a process based on these or a combination of these with a normal procedure, the title compound was respectively obtained.

4-(2-fluoro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

¹H-NMR(CD₃OD) δ : 3.23 (3H, s), 6.19 (1H, d, J = 2.3 Hz), 6.55 (1H, d, J = 2.3 Hz), 7.23 (1H, dd, J = 4.2, 2.1 Hz), 7.61-7.64 (2H, m), 7.67 (1H, dd, J = 8.6, 2.7 Hz), 7.84-7.85 (1H, m), 8.02

(1H, td, J = 7.8, 1.6 Hz), 8.09 (1H, d, J = 8-6 Hz), 8.16 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.68 (1H, d, J = 4-7 Hz).

ESI-MS (m/e): 478 (M+H).

6-(6-methanesulphonyl-pyridine-3-yloxy)-4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

1H-NMR (DMSO-d₆) δ : 3.25 (3H, s), 6.61-6.62 (2H, m), 6.97-7.00 (2H, m), 7.63-7.67 (2H, m), 8.02-8.11 (4H, m), 8.56 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 4-7 Hz), 10.33 (1H, s)

ESI-MS (m/e): 476 (M+H).

Example 273

4-(2-fluoro-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

2-fluoro-pyridin-3-ol and 4-methanesulphonyl-phenol were used successively, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

1H-NMR(CD₃OD) δ : 3.13 (3H, s), 6.67 (1H, d, J = 2.0 Hz), 7.21-7.25 (2H, m), 7.35-7.39 (2H, m), 7.60-7.63 (1H, m), 7.77-7.82 (1H, m), 7.95-7.97 (2H, m), 8.00-8.09 (2H, m), 8.36 (1H, d, J = 8.2 Hz), 8.83 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 477 (M+H).

Example 274

4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Step 1

Synthesis of 5-(4-ethanesulfonyl-phenoxy)-3-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-benzene-1,2-diamine

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-ethanesulphonyl-phenol were successively used, and, by the same process as in Example 67 (Step 1)-(Step 4), a process based on this or a combination of these with a normal procedure, the title compound was obtained as brown oily substance.

Step 2

Production of 4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using

5-(4-ethanesulfonyl-phenoxy)-3-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-benzene-1,2-diamine obtained in (Step 1), the title compound was obtained as a white solid by the same process

as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 3.65 (3H, s), 6.37 (1H, t, J = 7.2 Hz), 6.42 (1H, s), 7.09 (1H, s), 7.20 (2H, d, J = 8.8 Hz), 7.37 (1H, d, J = 6.6 Hz), 7.46-7.54 (1H, m), 7.55 (1H, d, J = 6.0 Hz), 7.88 (2H, d, J = 8.8 Hz), 7.94-8.02 (1H, m), 8.36 (1H, d, J = 7.6 Hz), 8.73 (1H, s).

ESI-MS (m/e): 503 (M+H).

Example 275

4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-(propane-2-sulfonyl)-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-(propane-2-sulfonyl)-phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

¹H-NMR(CD₃OD) δ : 1.27 (6H, d, J = 6.8 Hz), 3.27-3.38 (1H, m), 3.65 (3H, s), 6.37 (1H, t, J = 7.4 Hz), 6.42 (1H, s), 7.10 (1H, s), 7.20 (2H, d, J = 8.8 Hz), 7.35-7.45 (1H, m), 7.47-7.54 (1H, m), 7.55 (1H, d, J = 6.8 Hz), 7.85 (2H, d, J = 8.8 Hz), 7.27-8.03 (1H, m), 8.30-8.40 (1H, m), 8.74 (1H, s).

ESI-MS (m/e): 517 (M+H).

Example 276

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 268 and 1H-pyrazole-3-carboxaldehyde, the title compound was obtained by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 6.28-6.32 (1H, m), 7.09 (1H, s), 7.19 (2H, t, J = 8.2 Hz), 7.34 (1H, s), 7.52 (1H, t, J = 4.5 Hz), 7.83 (1H, s), 8.04 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.7 Hz).

ESI-MS(m/e): 498 (M+H).

Example 277

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-(N,N-dimethylamino sulfonyl)-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-(N,N-dimethylamino sulfonyl)-phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a pale yellow

solid.

¹H-NMR (DMSO-d₆) δ : 2.58 (6H, s), 3.48 (3H, s), 6.21 (1H, t, J = 7.1 Hz), 6.31 (1H, s), 6.91 (1H, s), 7.16 (2H, d, J = 8.8 Hz), 7.30 (1H, d, J = 6.4 Hz), 7.52 (1H, dd, J = 7.5, 5.7 Hz), 7.60 (1H, d, J = 5.1 Hz), 7.71 (2H, d, J = 8.8 Hz), 7.99 (1H, td, J = 7.8, 1.6 Hz), 8.27 (1H, d, J = 7.8 Hz), 8.73 (1H, d, J = 4.6 Hz).

ESI-MS(m/e): 518 (M+H).

Example 278

4-(2-chloro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Step 1

Synthesis of 3-(2-chloro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine 2-chlorophenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and the title compound was obtained as brown oily substance by the process of Example 67 (Step 1) to (Step 4), by a method based on this, or by combining these with the normal method.

Step 2

Production of 4-(2-chloro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-chloro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in (Step 1), the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 6.9 Hz), 3.39 (2H, q, J = 6.9 Hz), 6.28 (1H, d, J = 2.0 Hz), 7.10-7.20 (1H, m), 7.28-7.31 (2H, m), 7.39-7.43 (1H, m), 7.57 (2H, td, J = 8.3, 4.2 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79-8.80 (1H, m), 9.58 (1H, s).

ESI-MS(m/e): 508 (M+H).

Example 279

4-(2-fluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole 2-fluoro-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.40 (1H, s), 7.10-7.20 (1H, m), 7.28-7.34 (4H, m), 7.57 (1H, dd, J = 8.6, 2.7 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79-8.80 (1H, m), 9.56 (1H, s).

ESI-MS(m/e): 492 (M+H).

Example 280

4-(2-trifluoromethyl-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazine

-2-yl-1H-benzimidazole

2-trifluoromethyl-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4Hz), 3.40 (2H, q, J = 7.4Hz), 6.50 (1H, d, J = 2.0Hz), 7.24 (2H, d, J = 7.8Hz), 7.38 (1H, t, J = 7.8Hz), 7.59 (1H, dd, J = 8.6, 2.7Hz), 7.64 (1H, t, J = 7.6Hz), 7.81 (1H, d, J = 7.8Hz), 8.06 (1H, d, J = 8.6Hz), 8.50 (1H, d, J = 2.7Hz), 8.71 (1H, d, J = 2.3Hz), 8.78-8.79 (1H, m), 9.54-9.55 (1H, m)

ESI-MS(m/e): 542 (M+H).

Example 2814-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-cyclopropane sulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-cyclopropane sulphonyl phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a pale yellow solid.

¹H-NMR(DMSO-d₆) δ : 1.01-1.15 (4H, m), 2.81-2.90 (1H, m), 3.51 (3H, s), 6.24 (1H, t, J = 7.0 Hz), 6.35 (1H, d, J = 2.0 Hz), 6.95 (1H, d, J = 2.0 Hz), 7.18 (2H, d, J = 9.0 Hz), 7.33 (1H, dd, J = 7.5, 1.8 Hz), 7.53-7.57 (1H, m), 7.63 (1H, dd, J = 6.8, 1.8 Hz), 7.87 (2H, d, J = 9.0 Hz), 8.02 (1H, td, J = 7.8, 1.8 Hz), 8.31 (1H, d, J = 8.0 Hz), 8.75 (1H, d, J = 4.1 Hz).

ESI-MS(m/e): 515 (M+H).

Example 2824-(2,6-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-(1-methyl-pyrazol-3-yl)-1H-benzimidazole

Using 1H-1-methyl-pyrazole-3-carboxylic acid and 3-(2,6-difluoro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 268, the title compound was obtained by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 4.12 (3H, s), 6.61 (1H, s), 7.19 (1H, d, J = 2.3 Hz), 7.22 (1H, s), 7.25 (2H, dd, J = 5.6, 2.3 Hz), 7.37-7.43 (1H, m), 7.62 (1H, dd, J = 8.6, 2.7 Hz), 7.93 (1H, d, J = 2.3 Hz), 8.08-8.09 (1H, m), 8.51 (1H, d, J = 2.3 Hz).

ESI-MS(m/e): 512 (M+H).

Example 2834-(3-trifluoromethyl-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

3-trifluoromethyl-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the

same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.39 (1H, s), 7.25-7.37 (5H, m), 7.57 (1H, dd, J = 4.3, 2.2 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.7 Hz), 8.79 (1H, s), 9.56 (1H, s)

ESI-MS(m/e): 542 (M+H).

Example 284

4-(4-trifluoromethyl-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

4-trifluoromethyl-phenol and 6-ethane sulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.80 (1H, s), 7.32 (2H, d, J = 8.6 Hz), 7.66-7.64 (1H, m), 7.72 (2H, d, J = 8.6 Hz), 8.08 (1H, d, J = 9.0 Hz), 8.54-8.56 (1H, m), 8.70-8.73 (1H, m), 8.78 (1H, s), 9.50 (1H, s)

ESI-MS(m/e): 542 (M+H).

Example 285

4-(2,3-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

2,3-difluoro-phenol and 6-ethane sulphonyl-pyridin-3-ol were successively used, and the title compound was obtained by the same process as in Example 278, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.3 Hz), 3.40 (2H, q, J = 7.3 Hz), 6.59 (1H, d, J = 1.6 Hz), 7.12-7.18 (4H, m), 7.60 (1H, dd, J = 9.0, 2.7 Hz), 8.07 (1H, dd, J = 8.6, 0.8 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.79 (1H, dd, J = 2.7, 1.4 Hz), 9.53 (1H, d, J = 1.6 Hz).

ESI-MS(m/e): 510 (M+H).

Example 286

4-(2-cyano-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2-cyanophenol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 3.23 (3H, s), 6.86 (1H, d, J = 2.0 Hz), 7.21 (1H, d, J = 8.2 Hz), 7.33-7.37 (2H, m), 7.62-7.67 (3H, m), 7.84 (1H, d, J = 7.8 Hz), 8.04-8.11 (2H, m), 8.36 (1H, d, J = 7.8 Hz), 8.54 (1H, d, J = 2.7 Hz), 8.82 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 484 (M+H).

Example 2874-(2,4-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2,4-difluoro-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.11 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.51 (1H, d, J = 2.0 Hz), 7.05-7.10 (2H, m), 7.37-7.39 (1H, m), 7.46-7.59 (3H, m), 7.98-8.02 (2H, m), 8.26 (1H, d, J = 7.8 Hz), 8.56 (1H, d, J = 2.7 Hz), 8.73 (1H, d, J = 4.3 Hz)

ESI-MS(m/e): 509 (M+H).

Example 2884-(pyridin-2-ylsulphanyl)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Pyridine-2-thiol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as yellow solid.

¹H-NMR (CDCl₃) δ : 3.22 (3H, s), 7.03 (1H, d, J = 8.0 Hz), 7.06-7.10 (1H, m), 7.34 (1H, d, J = 2.1 Hz), 7.37-7.41 (1H, m), 7.43 (1H, dd, J = 8.8, 2.8 Hz), 7.52 (1H, td, J = 7.8, 2.2 Hz), 7.64 (1H, d, J = 2.1 Hz), 7.88 (1H, td, J = 7.8, 1.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.39 (1H, d, J = 7.8 Hz), 8.45 (1H, dd, J = 4.9, 1.0 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 4.1 Hz).

ESI-MS(m/e): 476 (M+H).

Example 2894-(2,6-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-5-fluoro-2-pyrazin-2-yl-1H-benzimidazole

2,6-difluoro-phenol, 6-ethane sulfonyl-pyridin-3-ol and pyrazine-2-carboxylic acid were successively used, and, by the same process as in Example 119, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale yellow solid.

¹H-NMR (CDCl₃) δ : 1.30 and 1.32 (total 3H, each t, J = 7.4 Hz), 3.38 and 3.40 (total 2H, each q, J = 7.4 Hz), 6.96-7.03 (2H, m), 7.10-7.20 (1H, m), 7.14 and 7.52 (total 1H, each d, J = 6.0 Hz), 7.34 and 7.38 (total 1H, each dd, J = 8.6, 2.8 Hz), 8.03 and 8.06 (total 1H, each d, J = 8.6 Hz), 8.48 and 8.52 (total 1H, each d, J = 2.8 Hz), 8.55-8.72 (2H, m), 9.38 and 9.62 (total 1H, each d, J = 1.5 Hz).

ESI-MS(m/e): 528 (M+H).

Example 2904-(2,6-difluoro-phenoxy)-6-(6-ethane
sulfonyl-pyridin-3-yloxy)-5-fluoro-2-pyridin-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-4-fluoro-5-(6-ethane sulfonyl-pyridin-3-yloxy) -benzene -1,2-diamine obtained in Example 289, the title compound was obtained as a brown solid by method of Example 196 (Step 6), a method based on this, or a combination of these with a normal method.

¹H-NMR (CDCl₃) δ : 1.30 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.94-7.01 (2H, m), 7.04-7.50 (4H, m), 7.79-7.95 (1H, m), 7.99-8.07 (1H, m), 8.23 and 8.37 (total 1H, each d, J = 7.0 Hz), 8.48 (1H, s), 8.60-8.68 (1H, m)

ESI-MS(m/e): 527 (M+H).

Example 2914-(2,6-difluoro-phenoxy)-6-(6-ethane
sulfonyl-pyridine-3-yloxy)-5-fluoro-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-4-fluoro-5-(6-ethanesulfonyl-pyridin-3-yloxy) benzene-1,2-diamine obtained in Example 289, and 1H-1-methyl-pyrazole-3-carboxylic acid, the title compound was obtained as a pale yellow solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.23 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 4.02 (3H, s), 6.94 (1H, s), 7.01-7.12 (2H, m), 7.14-7.23 (1H, m), 7.29 (1H, d, J = 5.4 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.70 (1H, s), 8.06 (1H, d, J = 8.6 Hz), 8.50 (1H, s)

ESI-MS(m/e): 530 (M+H).

Example 2924-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-5-fluoro-2-pyridin-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 290, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

¹H-NMR (CDCl₃) δ : 3.21 (3H, s), 6.98 (2H, t, J = 8.0 Hz), 7.05-7.50 (4H, m), 7.80-7.93 (1H, m), 8.03 (1H, t, J = 8.8 Hz), 8.23 and 8.37 (total 1H, each d, J = 8.4 Hz), 8.47 (1H, s), 8.61 and 8.67 (total 1H, each s).

ESI-MS(m/e): 513 (M+H).

Example 2931-(2-(6-(4-[2-hydroxy-ethyl]-phenoxy)-2-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-bromo phenethyl-alcohol, the title compound was obtained as a white solid the same method as in an example 122, a method based on this, or a combination of these with a normal method.

¹H-NMR (CDCl₃) δ : 1.05-2.90 (10H, m), 3.00-4.45 (4H, m), 5.20-5.45 (1H, m), 6.80-7.70 (7H, m), 7.85-7.95 (1H, m), 8.20-8.45 (1H, m), 8.50-8.80 (1H, m)

ESI-MS(m/e): 443 (M+H).

Example 294

1-(2-(6-(4-[5-methyl-[1,3,4]oxadiazol-2-yl]-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 2-(4-bromophenyl)-5-methyl-[1,3,4] oxadiazole, the title compound was obtained as a colourless oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.40-2.80 (10H, m), 3.50-3.95 (2H, m), 5.10-5.50 (1H, m), 6.90-7.60 (5H, m), 7.82-8.10 (3H, m), 8.35-8.45 (1H, m), 8.60-8.75 (1H, m).

ESI-MS(m/e): 481 (M+H).

Example 295

1-(2-(6-(4-[2-methyl-oxazol-5-yl]-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-(4-bromophenyl)-2-methyl-oxazole, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.66-2.66 (10H, m), 3.53-3.94 (2H, m), 5.21-5.57 (1H, m), 6.93-7.92 (9H, m), 8.30-8.69 (2H, m), 10.61-10.97 (1H, m)

ESI-MS(m/e): 480 (M+H).

Example 296

2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.84-2.16 (3H, m), 2.24-2.43 (1H, m), 3.12 and 3.14 (total 3H, each s), 3.49-4.24 (4H, m), 5.17-5.38 (1H, m), 7.20-7.58 (5H, m), 7.93-8.04 (3H, m), 8.26-8.30 (1H, m), 8.73 (1H, s)

ESI-MS(m/e): 493 (M+H).

Examples 297, 2981-(2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone.1-(2-(6-(5-chloro-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-chloro-2-ethane sulfonyl-pyridine, the title compounds were respectively obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

1-(2-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

¹H-NMR (CDCl₃) δ : 1.00-1.34 (3H, m), 1.44-2.41 (7H, m), 3.11-3.89 (4H, m), 5.05-5.47 (1H, m), 6.73-8.72 (9H, m), 10.89-11.47 (1H, m).

ESI-MS(m/e): 492 (M+H).

1-(2-(6-(5-chloro-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

¹H-NMR (CDCl₃) δ : 1.51-2.33 (7H, m), 3.41-3.90 (2H, m), 5.03-5.45 (1H, m), 6.79-8.67 (9H, m), 10.80-11.00 (1H, m).

ESI-MS(m/e): 434 (M+H).

Example 2995-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A and enantiomer BStep 1Synthesis of 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To 1 ml of a pyridine solution of 53 mg 1-(2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone obtained from Example 162 (Step 6) were added successively pyrazine-2-carboxylic acid 14.5 mg, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 27.0 mg, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was diluted with saturated aqueous sodium chloride solution and extraction was carried out with ethyl acetate. The organic layers were combined, and washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was dissolved in toluene 1 ml, and p-toluenesulfonic acid monohydrate 9.9 mg

was added, and the reaction liquor was stirred at 120°C for six hours. After cooling, the reaction liquor was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was refined by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1), and the title compound was obtained as oily substance.

Step 2

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole

To a solution of 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 40 mg dissolved in a mixture of methanol 1.6 ml and water 0.4 ml was added potassium carbonate 55 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was concentrated under reduced pressure, and saturated ammonium chloride aqueous solution was added to the residue and thereafter, it was extracted with chloroform and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and it was refined by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol/aqueous ammonia = 90/10/1) and the title compound was obtained as oily substance.

Step 3

Production of 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A and enantiomer B

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole 7.2 mg was optically-resolved on optical resolution column (CHIRALPAK AD 2cm phi x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: hexane/ethanol/diethylamine 20/80/0.1, flow rate 10 ml/min) and enantiomer A (retention time: 21.5 min), enantiomer B (retention time = 25.3 min) were respectively obtained as a yellow oily substance.

Example 300

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone Enantiomer A

Using 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A obtained in Example 299, the title compound was obtained as an oily substance by the same process as in Example 164, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.42 (7H, m), 3.00-3.09 (3H, m), 3.57-3.90 (2H, m), 5.10-5.43 (1H, m), 7.02-8.00 (6H, m), 8.57-8.73 (2H, m), 9.55-9.48 (1H, m).

ESI/MS(m/e): 478 (M+H).

Example 301

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B

Using 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 299, the title compound was obtained as an oily substance by the same process as in Example 164, a process based on this or a combination of these with a normal procedure.

ESI-MS(m/e): 478 (M+H).

Example 302

1-(2-(6-(6-[propane-2-sulfonyl]-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-chloro-2-(propane-2-sulfonyl)-pyridine, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.11-1.40 (6H, m), 1.55-2.43 (7H, m), 3.54-3.89 (3H, m), 5.11-5.48 (1H, m), 6.67-8.72 (9H, m), 11.00-11.69 (1H, m)

ESI-MS (m/e): 506 (M+H).

Example 303

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-phenyl-propan-1-one

Using 3-phenyl-propionic acid, the title compound was obtained as a colourless oily material by the same method as in an example 296, a method based on this, or a method which combined these and the normal method.

¹H-NMR (CDCl₃) δ : 1.10-3.10 (11H, m), 3.40-4.00 (2H, m), 4.90-5.30 (1H, m), 6.80-8.00 (13H, m), 8.30-8.50 (1H, m), 8.60-8.75 (1H, m), 10.50-11.20 (1H, m).

ESI-MS(m/e): 567 (M+H).

Example 304

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethane thione

To 1 ml of chloroform solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B 20mg obtained in Example 163,

ethyl dithioacetate 0.010 ml were added, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with chloroform, then washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and it was refined by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1), to obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 1.50-2.80 (7H, m), 3.00-3.20 (3H, m), 3.60-4.40 (2H, m), 5.30-5.50 (1H, m), 7.00-7.60 (5H, m), 7.80-8.00 (3H, m), 8.30-8.50 (1H, m), 8.60-8.75 (1H, m).

ESI-MS(m/e): 493 (M+H).

Example 305

2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using sodium fluoroacetate, the title compound was obtained by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.67-2.40 (4H, m), 3.00-3.13 (3H, m), 3.51-4.00 (2H, m), 4.48-5.06 (2H, m), 5.18-5.46 (1H, m), 7.02-7.69 (5H, m), 7.80-7.98 (3H, m), 8.34-8.44 (1H, m), 8.53-8.70 (1H, m), 10.82-11.12 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 306

1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Step 1

Synthesis of 4-bromo-5-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine

To N,N-dimethylformamide 50 ml solution of 4-bromo-5-fluoro-2-nitrophenyl amine 6.4 g, 4-methanesulphonyl-phenol 5.2 g, potassium carbonate 5.7 g were added successively, and the reaction liquor was stirred at 120°C for three hours. Water 200 ml was added to the reaction liquor and the precipitated solid was recovered by filtration and was dried, and the title compound was obtained as a brown solid.

Step 2

Synthesis of 2-(4-amino-2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1- carboxylic acid t-butyl ester

To a solution of 4-bromo-5-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine 10.3 g in dimethoxyethane 100 ml, 1-(t-butoxycarbonyl) pyrrole-2-boronic acid 7.9 g, dichlorobis triphenyl phosphine palladium 1.8 g, saturated sodium carbonate aqueous solution 50 ml and water 50 ml

were added successively, and under a nitrogen atmosphere, the reaction liquor was stirred at 80°C for one hour. After cooling, the reaction liquor was filtered with cellite, and the filtrate was diluted with ethyl acetate, and washed successively with water, saturated aqueous sodium chloride solution and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained as brown oily substance.

Step 3

Synthesis of 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester

To a solution of 2-(4-amino-2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 12g in 2-propanol 200 ml, water 20 ml, 5 % platinum-carbon catalyst 4 g were added, and the reaction liquor was stirred at 70°C under hydrogen pressure atmosphere of 50 kgf/cm² for two days. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as dark brown oily substance.

Step 4

Synthesis of 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole

To solution of 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 500 mg in pyridine 10 ml were successively added 5-bromopyridine-2-carboxylic acid 220 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 260 mg, and the reaction liquor was stirred at room temperature for 12 hours. The reaction liquor was diluted with chloroform, and it was washed successively with water, saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was dissolved in trifluoroacetic acid 10 ml, and the reaction liquor was heated under reflux for three hours. After cooling, the reaction liquor was distilled off under reduced pressure, and the obtained residue was diluted with chloroform, and it was made basic with saturated aqueous sodium bicarbonate, then, the organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent : chloroform/methanol/aqueous ammonia = 50/1/0.1) and the title compound was obtained as a colourless oily substance.

Step 5

Production of 1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To solution of 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole 220 mg in pyridine 2 ml, was added acetic anhydride 0.050 ml, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (chloroform/methanol/aqueous ammonia = 50/1/0.1), and the title compound was obtained as pale-brown solid.

¹H-NMR (CDCl₃) δ : 1.60-2.40 (7H, m), 2.90-3.15 (3H, m), 3.50-3.90 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.05 (3H, m), 8.20-8.35 (1H, m), 8.60-8.80 (1H, m), 10.50-11.05 (1H, m)

ESI-MS(m/e): 555, 557 (M+H).

Example 307

1-(2-(2-(6-fluoro-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester and 6-fluoro-pyridine-2-carboxylic acid, the title compound was obtained the same process as in Example 306 (Step 4) (Step 5), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.70-2.40 (7H, m), 2.98-3.11 (3H, m), 3.57-3.90 (2H, m), 5.07-5.51 (1H, m), 6.81-8.32 (9H, m), 10.64-11.36 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 308

1-(2-(2-pyridin-2-yl)-6-(6-trifluoromethyl-pyridin-3-yloxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-bromo-2-trifluoromethyl-pyridine, the title compound was obtained as a pale yellow solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.89 and 2.14 (total 3H, each s), 1.90-2.20 (3H, m), 2.24-2.50 (1H, m), 3.63-3.99 (2H, m), 5.26-5.40 (1H, m), 7.34-7.63 (4H, m), 7.80-7.86 (1H, m), 7.94-8.02 (1H, m), 8.29-8.37 (1H, m), 8.58-8.59 (1H, m), 8.73-8.78 (1H, m).

ESI-MS(m/e): 468 (M+H).

Example 3091-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone Enantiomer A**Step 1**Synthesis of 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone 2.2 g obtained from Example 121 (Step 8) were optically-resolved on column for optical resolution (CHIRALPAK AS 2cm phi x 25 cmL (Daicel Chemical Industries Ltd), mobile phase: hexane/ethanol 30/70, flow rate: 15 ml/min), and enantiomer A (retention time = 11.43min), enantiomer B (retention time = 16.32min) were respectively obtained as black solids.

Step 2Production of 1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A

Using the 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer A obtained from Example 309 (Step 1) and 5-chloro-2-methanesulphonyl-pyridine, the title compound was obtained as an oily substance by the process of Example 121 (Step 9) - (Step 12), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.42 (7H, m), 3.16-3.27 (3H, m), 3.57-3.91 (2H, m), 5.14-5.34 (1H, m), 7.04-8.10 (6H, m), 8.31-8.70 (3H, m), 10.59-10.94 (1H, m).

ESI-MS(m/e): 478 (M+H).

Example 3101-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B

Using the 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer B obtained from Example 309 (Step 1), the title compound was obtained as an oily substance by the same process as in Example 309, a process based on this or a combination of these with a normal procedure.

ESI-MS(m/e): 478 (M+H).

Example 311(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-pyridin-2-yl-methanone

Using pyridine-2-carboxylic acid and 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained by the same process as in Example 296, a process based on this or a

combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.60-2.45 (4H, m), 2.91-3.09 (3H, m), 3.71-4.30 (2H, m), 5.44-5.60 and 5.91-6.03 (total 1H, each m), 6.77-7.93 (11H, m), 8.10-8.66 (3H, m), 10.82-11.00 (1H, m).

ESI-MS(m/e): 540 (M+H).

Example 312

(2-fluoro-phenyl)-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-methanone

Using 2-fluorobenzoic acid and 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.51 (4H, m), 2.90-3.08 (3H, m), 3.40-4.08 (2H, m), 4.91-5.02 and 5.46-5.60 (total 1H, each m), 6.55-8.69 (15H, m)

ESI-MS(m/e): 557 (M+H).

Example 313

6-(1-acetyl pyrrolidin-2-yl)-5-(4-fluoro phenoxy)-2-isoxazol-3-yl-1H-benzimidazole

Using isoxazole-3-carbaldehyde, the title compound was obtained by the same process as in Example a process based on this or a combination of these with a normal procedure process same as Example 189, this, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.46 (4H, m), 1.87 and 2.16 (total 3H, eachs), 3.58-3.88 (2H, m), 5.13-5.17 and 5.52-5.55 (total 1H, each m), 6.85-7.40 (7H, m), 8.56 (1H, s).

ESI-MS(m/e): 407 (M+H).

Example 314

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2- carbonitrile

Using the 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer B obtained from Example 309 (Step 1) and 2-cyano-5-bromo-pyridine, the title compound was obtained as a white solid by the same process as in Example 309, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.53-2.42 (7H, m), 3.40-3.50 (2H, m), 5.07-5.29 (1H, m), 7.00-7.94 (6H, m), 8.28-8.68 (3H, m), 11.00-11.52 (1H, m).

ESI-MS(m/e): 425 (M+H).

Example 315

(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-methyl-carbamic acid t-butyl ester

Using N-t-butoxycarbonyl-glycine and 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-

pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.20-1.69 (16H, m), 2.76-3.12 (7H, m), 5.15-5.26 (1H, m), 7.00-7.44 (5H, m), 7.76-8.00 (4H, m), 8.28-8.40 (1H, m), 8.58-8.73 (1H, m).

ESI-MS(m/e): 606 (M+H).

Example 316

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylamino-ethanone

Using (2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-methyl-carbamic acid t-butyl ester obtained in Example 315, the title compound was obtained by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-1.97 (4H, m), 2.20-2.46 (3H, m), 2.94-3.08 (5H, m), 3.19-3.90 (2H, m), 5.15-5.43 (1H, m), 7.08-7.65 (5H, m), 7.87-7.94 (3H, m), 8.36-8.38 (1H, m), 8.64 (1H, s).

ESI-MS(m/e): 506 (M+H).

Example 317

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Step 1

Synthesis of 2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid t-butyl ester

To solution of the 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained from Example 306 (Step 3), 49.0 mg, in N,N-dimethylformamide 1 ml was added 1H-pyrazole-3-carboxaldehyde 10.0 mg, and the reaction liquor was stirred at 90°C one overnight. After cooling, the reaction liquor was diluted with ethyl acetate and was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1) and the title compound was obtained as a brown solid.

Step 2

Production of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidine-1-c

arboxylic acid t-butyl ester 49.2 mg was dissolved in 4N hydrochloric acid-dioxane 1 ml, and the reaction liquor was stirred at room temperature for two hours. Reaction solvent was eliminated by distillation under reduced pressure, and acetic anhydride 0.012 ml was added to a solution of the obtained residue in pyridine 2 ml, and the mixture was stirred at room temperature for 30 minutes. Reaction solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1) and the title compound was obtained as a brown solid. ¹H-NMR (CDCl₃) δ : 1.53-2.38 (7H, m), 2.97-3.10 (3H, s), 3.39-3.99 (2H, m), 5.06-5.31 (1H, m), 6.80-8.04 (8H, m).
ESI-MS(m/e): 466 (M+H).

Example 318

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using the 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl) -pyrrolidine-1- carboxylic acid t-butyl ester obtained from Example 306 (Step 3) and 1-methyl-1H-pyrazole-3-carboxylic acid, the title compound was obtained as a white solid by the same process as Example 306 (Step 4), (Step 5), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.70-2.37 (7H, m), 2.98-3.11 (3H, m), 3.52-4.02 (5H, m), 5.04-5.43 (1H, m), 6.74-7.67 (6H, m), 7.79-7.97 (2H, m), 10.38-11.00 (1H, m).

ESI-MS(m/e): 480 (M+H).

Example 319

1-(2-(2-(5-fluoro-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone.

Using 5-fluoro-pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 318, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.50 (7H, m), 2.85-3.20 (3H, m), 3.50-4.00 (2H, m), 5.00-5.50 (1H, m), 6.80-8.10 (7H, m), 8.20-8.60 (2H, m), 10.50-11.20 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 320

(1-amino-cyclopropyl)-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-methanone

Using 1-amino-cyclopropanecarboxylic acid, the title compound was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 0.80-1.10 (4H, m), 1.88-2.17 (3H, m), 2.32-2.40 (1H, m), 3.12 (3H, s), 4.06 (2H, brs), 5.21 (1H, brs), 7.18-7.54 (5H, m), 7.91-7.99 (3H, m), 8.27 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 4.3 Hz).

ESI-MS(m/e): 518 (M+H).

Example 321

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile

Using 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer B obtained in Example 309 (Step 1) and pyrazine-2-carboxaldehyde, the title compound was obtained as an oily substance by the same process as in Example 314, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.67-2.47 (7H, m), 3.60-3.92 (2H, m), 5.11-5.35 (1H, m), 7.00-7.77 (4H, m), 8.47-8.73 (3H, m), 9.52-9.68 (1H, m), 10.88-11.94 (1H, m).

ESI-MS(m/e): 426 (M+H).

Example 322

1-(2-(2-(5-cyano-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-cyano-pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.05-2.40 (7H, m), 2.80-3.20 (3H, m), 3.60-4.00 (2H, m), 5.05-5.45 (1H, m), 6.90-7.80 (4H, m), 7.80-8.00 (2H, m), 8.05-8.20 (1H, m), 8.40-8.60 (1H, m), 8.80-9.00 (1H, m), 10.40-10.80 (1H, m).

ESI-MS(m/e): 502 (M+H).

Example 323

1-(2-(2-(4-chloro-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-chloro-pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.67-2.40 (7H, m), 3.00-3.13 (3H, m), 3.54-3.91 (2H, m), 5.10-5.44 (1H, m), 6.79-7.52 (5H, m), 7.64-7.97 (2H, m), 8.36-8.57 (2H, m), 10.75-11.24 (1H, m).

ESI-MS(m/e): 511 (M+H).

Example 324

1-(2-(2-(5-ethoxy-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

din-1-yl)-ethanone

Using 5-ethoxy-pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.00-3.40 (10H, m), 3.60-4.00 (3H, m), 4.20-5.20 (4H, m), 5.80-6.40 (1H, m), 7.20-9.20 (9H, m), 11.50-12.00 (1H, m).

ESI-MS(m/e): 521 (M+H).

Example 325Trans-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanoneStep 1Synthesis of 1-(2-fluoro-4-nitro-phenyl)-3-butene-1-ol

To a solution of 4-nitro-2-fluoro-benzaldehyde (synthesised according to process described in US6239152) 2.00 g in chloroform 12 ml, was added titanium tetrachloride 0.65 ml, and the reaction liquor was stirred at room temperature for ten minutes, and thereafter, allyl-trimethyl-silane 2.4 ml was added, and the reaction liquor was stirred at room temperature for 20 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained as reddish yellow solid.

Step 2Synthesis of N-(1-(2-fluoro-4-nitro-phenyl)-3-butenyl)-acetamide

To solution of 1-(2-fluoro-4-nitro-phenyl)-3-butene-1-ol 480 mg in chloroform 10 ml were added, methanesulfonyl chloride 0.29 ml and triethylamine 0.63 ml, and thereafter the reaction liquor was stirred at room temperature for 15 minutes. The reaction liquor was washed using water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and crude product was obtained as pale yellow oily substance. To solution of crude product in dimethylformamide 10 ml was added sodium azide 310 mg, and the reaction liquor was stirred at 45°C for 30 minutes. The reaction liquor was diluted with ethyl acetate and was washed using water, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and crude product was obtained as brown oily substance. To solution of the obtained crude product in tetrahydrofuran 10 ml were added triphenyl phosphine 1.0 g and water 2 ml, and the reaction liquor was stirred while heating under reflux for 12 hours. 1 N hydrochloric acid was added to the reaction liquor, and the organic layer was eliminated, and thereafter the aqueous layer was made basic using 1N sodium hydroxide

aqueous solution. Extraction with chloroform was carried out, and it was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and crude product 380 mg was obtained as brown oily substance. To solution of crude product 380 mg in chloroform 10 ml were added triethylamine 0.50 ml, acetic anhydride 0.25 ml and 4-dimethylaminopyridine 20 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol 50/1) and the title compound was obtained as brown oily substance.

Step 3

Synthesis of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4-hydroxy-pyrrolidine

To solution of N-(1-(2-fluoro-4-nitro-phenyl)-3-butenyl)-acetamide 200 mg in tetrahydrofuran 4 ml were added water 1 ml and iodine 600 mg, then the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with chloroform, and it was washed successively with saturated aqueous sodium bicarbonate, saturated sodium thiosulfate aqueous solution, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To solution of crude product in chloroform 5 ml were added triethylamine 0.25 ml, acetic anhydride 0.13 ml and 4-dimethylaminopyridine 10 mg, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and potassium carbonate 20 mg was added to methanol 5 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 30/1) and the title compound was obtained as diastereomer mixture of colourless solid.

Step 4

Synthesis of 1-acetyl-2-(2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine

Acetic anhydride 0.06 ml was added to pyridine 2 ml solution of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4-hydroxy-pyrrolidine 140 mg, and the reaction liquor was stirred overnight at 50°C. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate) and product 150 mg was obtained. Expanded Raney nickel catalyst about 50 mg was added to methanol 3 ml solution of product 57 mg, and the reaction liquor was stirred under a hydrogen atmosphere for 30 minutes, and thereafter, catalyst was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure. Pyridine-2-carboxylic acid 30 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 50 mg were added to

pyridine 2 ml solution of the residue, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

Step 5

Synthesis of trans-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine and cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine
Fuming nitric acid 0.1ml was added to trifluoroacetic acid 0.5 ml solution of 1-acetyl-2-(2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine 36 mg, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and thereafter the residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 15/1) and diastereomer mixture 30 mg of the title compound was obtained as a white solid. It was refined further by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 15/1) and single diastereomers of the title compound were respectively obtained as yellow solid. (Rf value = trans isomer > cis isomer).

Step 6

Production of trans-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

4-methanesulphonylphenol 10 mg and cesium carbonate 20 mg were added to dimethylformamide 0.5 ml solution of trans-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine 21 mg, and the reaction liquor was stirred at 90°C for one hour. Tin (II) chloride dihydrate 100 mg was added, and the reaction liquor was stirred at 90°C for five hours. The reaction liquor was diluted with ethyl acetate, and it was washed successively using water, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

¹H-NMR(CD₃OD) δ : 1.50-1.90 (3H, m), 2.10-2.53 (2H, m), 2.98 (3H, s), 3.60-3.90 (2H, m), 5.13-5.26 (2H, m), 7.03-7.65 (5H, m), 7.78-7.87 (3H, m), 8.10-8.18 (1H, m), 8.59 (1H, s).

ESI-MS(m/e): 535 (M+H).

Example 326

Trans-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-ethanone

25 % sodium methoxide 0.015 ml was added to solution of trans-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 325) 40 mg in methanol 2 ml, and the reaction liquor was stirred at room temperature for ten minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (YMC Corporation) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The title compound was obtained as a white solid by eliminating the solvent by distillation under reduced pressure.

¹H-NMR(CD₃OD) δ : 1.48-2.80 (5H, m), 2.99-3.10 (3H, m), 3.48-4.10 (2H, m), 4.40-4.60 (1H, m), 5.25-5.50 (1H, m), 7.00-7.50 (5H, m), 7.75-8.00 (3H, m), 8.24-8.48 (1H, m), 8.48-8.70 (1H, m), 10.70-11.20 (1H, m).

ESI-MS(m/e): 493 (M+H).

Example 327

Cis-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Bis (2-methoxyethyl) amino sulphur tri fluoride 0.02 ml was added to a solution of trans-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 326) 10 mg in chloroform 1 ml, and the reaction liquor was stirred at room temperature for ten minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 15/1) and the title compound was obtained as a white solid.

¹H-NMR(CD₃OD) δ : 1.92 (3H x 1/2, s), 2.22 (3H x 1/2, s), 2.22-2.80 (2H, m), 3.13 (3H x 1/2, s), 3.15 (3H x 1/2, s), 3.80-4.40 (2H, m), 5.20-5.50 (2H, m), 7.20-7.80 (5H, m), 7.90-8.10 (3H, m), 8.28 (1H, t, J = 7.8 Hz), 8.74 (1H, brs).

ESI-MS(m/e): 495 (M+H).

Example 328

Cis-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using the cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained from Example 325 (Step 5), the title compound was obtained as a colourless solid by the same process as Example 325 (Step 6), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.40-1.90 (3H, m), 2.20-2.55 (2H, m), 3.00 (3H, s), 3.62-3.90 (2H, m),

5.12-5.28 (2H, m), 6.98-7.75 (5H, m), 7.78-7.88 (3H, m), 8.11-8.19 (1H, m), 8.60 (1H, s).

ESI-MS(m/e): 535 (M+H).

Example 329

Cis-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using cis-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 328, the title compound was obtained as a colourless solid by the same process as in Example 326, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.80-2.00 (3H, m), 2.04-2.75 (2H, m), 3.12-3.16 (3H, m), 3.40-4.00 (2H, m), 4.45-4.55 (1H, m), 5.25-5.43 (1H, m), 7.18-7.42 (3H, m), 7.50-7.59 (1H, m), 7.62-7.77 (1H, m), 7.90-8.08 (3H, m), 8.24-8.32 (1H, m), 8.75-8.81 (1H, 1).

ESI-MS(m/e): 493 (M+H).

Example 330

Trans-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using cis-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone, the title compound was obtained as a pale yellow solid by the same process as in Example 327, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.70-2.73 (5H, m), 3.11-3.37 (3H, m), 3.62-4.51 (2H, m), 5.24-5.45 (2H, m), 7.13-7.76 (5H, m), 7.94-8.00 (3H, m), 8.28-8.33 (1H, m), 8.73-8.79 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 331

1-(4-oxo-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Dimethylsulfoxide 0.003 ml was added to a solution of oxalyl chloride 0.003ml in chloroform 1 ml at -50°C, and the reaction liquor was stirred at the same temperature for five minutes. A solution of trans-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 326, 6.7 mg in chloroform 1 ml was added to the reaction liquor, and thereafter the reaction liquor was stirred at -50°C for 15 minutes. Triethylamine 0.02 ml was added, and the reaction liquor was stirred at room temperature for five minutes, and thereafter the reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The

solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CtC (YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The title compound was obtained as a white solid by eliminating the solvent by distillation under reduced pressure.

¹H-NMR(CD₃OD) δ : 2.03 (3H, s), 2.68 (2H, s), 3.16 (3H, s), 4.09-4.22 (2H, m), 5.70-5.77 (1H, m), 7.05-7.80 (5H, m), 7.94-8.01 (3H, m), 8.24-8.32 (1H, m), 8.72-8.77 (1H, m).

ESI-MS(m/e): 491 (M+H).

Example 332

1-(4,4-difluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Step 1

Synthesis of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4,4-difluoro-pyrrolidine

Dimethylsulfoxide 0.035 ml was added to a solution of oxalyl chloride 0.035ml in chloroform 3 ml, at -50°C, and the reaction liquor was stirred at the same temperature for five minutes. A solution of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4-hydroxy-pyrrolidine 40 mg obtained in Example 325 (Step 3) in chloroform 2 ml was added to the reaction liquor, and thereafter the reaction liquor was stirred at 50°C for ten minutes. Triethylamine 0.10 ml was added, and the reaction liquor was stirred at room temperature for five minutes, and thereafter the reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and bis (2-methoxyethyl) amino sulphur trifluoride 0.06 ml was added to solution of the obtained residue in chloroform 1 ml, and the reaction liquor was stirred overnight at 70°C. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained.

Step 2

Production of 1-(4,4-difluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4,4-difluoro-pyrrolidine obtained in (Step 1), the title compound was obtained as a white solid by the process of Example 325 (Step 4)-(Step 6), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 2.03 (3H x 1/2, s), 2.05 (3H x 1/2, s), 2.50-2.63 (1H, m), 2.85-3.15 (1H, m), 3.14 (3H x 1/2, s), 3.15 (3H x 1/2, s), 3.95-4.25 (2H, m), 5.44-5.58 (1H, m), 7.22-7.29 (2H,

m), 7.26-7.42 (1H, m), 7.48-7.54 (1H, m), 7.61-7.68 (1H, m), 7.94-8.04 (3H, m), 8.26-8.32 (1H, m), 8.72-8.77 (1H, m).

ESI-MS(m/e): 513 (M+H).

Example 333

Cis-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

Racemic cis-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 327 45 mg was optically resolved on optical resolution column (CHIRALPAK AD 2cm phi x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: hexane/2-propanol 30/70, flow rate 10 ml/min), and enantiomer A (retention time = 18 min), enantiomer B (retention time = 22 min) were respectively obtained as white-color solids.

Enantiomer A

ESI-MS(m/e): 495 (M+H).

Enantiomer B.

ESI-MS(m/e): 495 (M+H).

Example 334

6-(6-(1-acetyl-pyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazol-2-yl)-nicotinic acid methyl ester

Using pyridine-2,5-dicarboxylic acid-5-methyl ester, the title compound was obtained as yellow solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

¹H-NMR/ (CDCl₃) δ : 1.20-2.40 (7H, m), 2.80-3.20 (3H, m), 3.40-4.00 (2H, m), 3.99 (3H, s), 5.05-5.45 (1H, m), 6.80-7.80 (4H, m), 7.80-8.05 (2H, m), 8.35-8.60 (2H, m), 9.10-9.30 (1H, m), 10.60-11.30 (1H, m).

ESI-MS(m/e): 535 (M+H).

Example 335

6-(6-(1-acetyl-pyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazol-2-yl)-nicotinic acid

Using 6-(6-(1-acetyl-pyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazol-2-yl)-nicotinic acid methyl ester obtained in Example 334, the title compound was obtained as pale yellow solid by same process as Example 121 (Step 6), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 1.60-2.60 (7H, m), 3.21 (3H, s), 3.60-4.00 (2H, m), 5.00-5.20 (1H, m), 6.90-7.60 (4H, m), 7.80-8.00 (2H, m), 8.30-8.60 (2H, m), 9.20 (1H, s).

ESI-MS(m/e): 521 (M+H).

Example 336

2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid dimethyl amide

Step 1

Synthesis of 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-2,3-dihydro-1H- benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid 4-nitro-phenyl ester

Triethylamine 0.060 ml and 4-nitrobenzoyl chloride 21 mg were added successively to tetrahydrofuran 1 ml solution of 5-(4-methanesulphonyl-phenoxy)-2- pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B 37mg obtained in Example 163, and the reaction liquor was stirred overnight at room temperature. Reaction solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as a white solid.

Step 2

Production of 2-(6-(4-methanesulphonyl-phenoxy)-2- pyridin-2-yl-3H- benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid dimethyl amide

Dimethylamine (2.0M tetrahydrofuran solution) 1 ml was added to tetrahydrofuran 1 ml solution of 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl- 2,3-dihydro-1H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid 4-nitro-phenyl ester 20 mg, and the reaction liquor was stirred overnight at 100°C in sealed tube. Reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid). The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate.

By eliminating the solvent under reduced pressure, the title compound was obtained as a white solid.

¹H-NMR(CD₃OD) δ : 1.80-1.92 (2H, m), 1.94-2.07 (1H, m), 2.33-2.42 (1H, m), 2.80 and 2.85 (total 6H, each brs), 3.12 (3H, s), 3.52-3.58 (1H, m), 3.62-3.78 (1H, m), 5.19-5.26 (1H, m), 7.16-7.80 (5H, m), 7.91-7.99 (3H, m), 8.27 (1H, d, J = 7.6 Hz), 8.73 (1H, brs).

ESI-MS(m/e): 506 (M+H).

Example 3371-(2-(2-(6-hydroxy-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-hydroxy-pyridine-2-carboxylic acid, the title compound was obtained as yellow solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.75-2.47 (7H, m), 2.97-3.26 (4H, m), 3.44-3.96 (2H, m), 5.20-5.40 (1H, m), 6.60-8.05 (10H, m).

ESI-MS(m/e): 493 (M+H).

Example 3381-(2-(6-(4-fluoro-phenylsulphanyl)-2-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**Step 1**Synthesis of 2-(4-amino-2-fluoro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester

1-(t-butoxy carbonyl) pyrrole-2-boron acid 1.6 g, tetrakis triphenylphosphine palladium 200 mg, saturated sodium carbonate aqueous solution 5 ml and water 5 ml were added successively to a solution of 4-bromo-3-fluoro-phenylamine 1 g in dimethoxyethane 1 ml, and the reaction liquor was stirred at 70°C for three hours under a nitrogen atmosphere. After cooling, the reaction liquor was filtered with celite, and the filtrate was diluted with ethyl acetate and washed successively with water and saturated aqueous sodium chloride solution and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1) and the title compound was obtained as pale-brown solid.

Step 2Synthesis of 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester.

Water 5 ml, 5 % platinum-carbon catalyst 660 mg were added to a solution of 2-(4-amino-2-fluoro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 2.2g in 2-propanol 50 ml, and, under hydrogen pressure atmosphere of 50 kgf/cm², it was stirred at 50°C for one day. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained as brown oily substance.

Step 3Synthesis of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-3-fluoro-phenyl)-amide

Pyridine-2-carboxylic acid 90 mg, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide

monohydrochloride 190 mg were added successively to solution of 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 181 mg in pyridine 2 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was diluted with chloroform, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and 4N hydrochloric acid-dioxane solution 2 ml were added to the obtained residue 300 mg, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with chloroform, and it was made basic with saturated aqueous sodium bicarbonate, then the organic layer was washed using saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and acetic anhydride 0.020 ml was added to pyridine 1 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for 20 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 50/1) and the title compound was obtained as yellow solid.

Step 4

Synthesis of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-5-fluoro-2-nitro-phenyl)-amide

Potassium nitrate 94 mg was added to solution of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-3-fluoro-phenyl)-amide in trifluoroacetic acid 3 ml, and the reaction liquor was stirred at room temperature for two days. The reaction liquor was concentrated down by distillation under reduced pressure, then diluted with chloroform, made basic with saturated aqueous sodium bicarbonate. Then extraction was carried out with chloroform. The organic layers were combined and were washed with saturated aqueous sodium chloride solution and were dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 50/1) and the title compound was obtained as a pale yellow solid.

Step 5

Production of 1-(2-(6-(4-fluoro-phenyl) sulphanyl)-2-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

4-fluoro-benzene thiol 20 mg, potassium carbonate 30 mg were added successively to solution of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-5-fluoro-2-nitro-phenyl)-amide 50 mg in N,N-dimethylformamide 1 ml, and the reaction liquor was stirred at 100°C for two hours. Tin (II)

chloride dihydrate 30 mg was added to the reaction liquor, and the reaction liquor was stirred at 100°C for a further three hours. After cooling, the reaction liquor was diluted using saturated aqueous sodium bicarbonate, extracted with chloroform, and the organic layer were dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. It was refined by preparative thin layer chromatography and the title compound was obtained as a white solid.

¹H-NMR (CDCl₃) δ : 1.60-2.50 (7H, m), 3.60-4.00 (2H, m), 5.20-5.80 (1H, m), 6.90-7.10 (2H, m), 7.15-7.80 (5H, m), 7.80-8.00 (1H, m), 8.30-8.45 (1H, m), 8.55-8.70 (1H, m), 10.60-11.20 (1H, m).

ESI-MS(m/e): 433 (M+H).

Example 339

1-(2-(6-(4-methanesulphonyl-phenylsulphanyl)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-methanesulphonyl-benzene thiol, the title compound was obtained as a white solid by same process as Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.40-2.45 (7H, m), 2.80-3.20 (3H, m), 3.50-4.00 (2H, m), 5.20-5.65 (1H, m), 7.10-8.25 (8H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m), 10.60-11.40 (1H, m).

ESI-MS(m/e): 493 (M+H).

Example 340

N-(5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide

Step 1

Synthesis of 1-(2-(6-(6-amino-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

5-bromo-2-nitro-pyridine 53.5 mg, cesium carbonate 84.2 mg, copper (II) oxide 25 mg were added to a solution of 1-(2-(6-hydroxy-2-pyridin-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) 55.0 mg in pyridine 1 ml, and the reaction liquor was stirred overnight at 120°C in sealed tube. After cooling, saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution were added successively to the reaction liquor, extraction was carried out ethyl acetate and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and hydrazine monohydrate 0.016 ml, expanded Raney nickel catalyst 20 mg were added to solution of the obtained residue in ethanol 2 ml, and the reaction liquor was stirred at room temperature for 30 minutes. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced

pressure. The obtained residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1) and the title compound was obtained as a yellow oily substance.

Step 2

Production of N-(5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide

Acetic anhydride 0.005 ml was added to a solution of 1-(2-(6-(6-amino-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 13.7 mg in pyridine 1 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor concentrated down by distillation under reduced pressure, and the obtained residue was dissolved in trifluoroacetic acid 1 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was concentrated down by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid) and silica gel column chromatography (eluent: chloroform / methanol = 9/1) and the title compound was obtained as an oily substance.

¹H-NMR (CDCl₃) δ : 1.64-2.44 (10H, m), 3.57-3.91 (2H, m), 5.26-5.62 (1H, m), 6.76-8.74 (10H, m), 10.59-11.31 (1H, m).

ESI-MS(m/e): 457 (M+H).

Example 341

1-(2-(6-(6-acetyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(5-bromo-pyridin-2-yl)-ethanone, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.66-2.42 (7H, m), 2.59-2.74 (3H, m), 3.51-3.90 (2H, m), 5.12-5.45 (1H, m), 6.85-8.10 (6H, m), 8.30-8.70 (3H, m), 10.86-11.24 (1H, m).

ESI-MS(m/e): 442 (M+H).

Example 342

2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A and enantiomer B

Racemic 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole 100 mg obtained in Example 306 was optically-resolved on optical resolution column (CHIRALPAK AD 2cm phi x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: hexane/isopropanol/diethylamine 20/80/0.1, flow rate 10 ml/min), and enantiomer A (retention

time = 24 min), enantiomer B (retention time = 27 min) were respectively obtained as oily substance.

Example 343

1-(2-(2-[5-bromo-pyridin-2-yl]-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A

Acetic anhydride 0.020 ml was added to solution of 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A (obtained in Example 342) 43mg in pyridine 1 ml, and the reaction liquor was stirred at room temperature for ten minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, it was extracted with chloroform, and the organic layer was dried with anhydrous magnesium sulphate and the solvent was eliminated by distillation under reduced pressure. It was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as a white solid. 1H-NMR (CDC13) δ : 1.60-2.40 (7H, m), 2.80-3.20 (3H, m), 3.50-3.95 (2H, m), 5.05-5.45 (1H, m), 6.90-7.80 (5H, m), 7.80-8.00 (2H, m), 8.10-8.30 (1H, m), 8.60-8.80 (1H, m). ESI/MS(m/e): 555, 557 (M+H).

Example 344

1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B

Using 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 342, the title compound was obtained as a white solid by the same process as in Example 343, a process based on this or a combination of these with a normal procedure.

Example 345

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(5-vinyl-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-vinyl-pyridine-2-carboxylic acid, the title compound was obtained as yellow solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.20-2.40 (7H, m), 2.90-3.15 (3H, m), 3.50-3.90 (2H, m), 5.00-5.45 (1H, m), 5.48 (1H, dd, J = 5.6, 11.2 Hz), 5.94 (1H, dd, J = 5.6, 17.6 Hz), 6.70-6.85 (1H, m), 7.00-7.25 (2H, m), 7.25-7.80 (2H, m), 7.80-8.00 (3H, m), 8.30-8.40 (1H, m), 8.55-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS(m/e): 503 (M+H).

Example 346

1-(2-(6-(6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Methylolithium (1.0M diethyl ether solution) 0.1 ml was added to solution of 1-(2-(6-(6-acetyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 341) 15.0 mg in tetrahydrofuran 1.5 ml solution at -78°C, and the reaction liquor was stirred at -78°C for 30 minutes. The reaction liquor was discharged into saturated ammonium chloride aqueous solution, extracted with chloroform and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform-methanol = 7.5/1) and the title compound was obtained as yellow solid.

¹H-NMR (CDCl₃) δ : 1.46-1.63 (6H, m), 1.63-2.47 (7H, m), 2.87-2.99 and 3.34-3.91 (total 3H, each m), 5.18-5.51 (1H, m), 6.72-7.91 (6H, m), 8.17-8.68 (3H, m), 10.54-10.94 (1H, br).

ESI-MS(m/e): 458 (M+H).

Example 347

(5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-carbamic acid ethyl ester

Ethyl chloroformate 0.003ml was added to solution of 1-(2-(6-(6-amino-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 340 (Step 1) 14.4 mg in pyridine 1 ml, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was concentrated down by distillation under reduced pressure, and the obtained residue was dissolved in trifluoroacetic acid 1 ml, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was concentrated down by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (YMC Co) mobile phase : water-acetonitrile-0.1% trifluoroacetic acid) and silica gel column chromatography (eluent: chloroform-methanol = 9/1) and the title compound was obtained as a yellow oily substance.

¹H-NMR (CDCl₃) δ : 1.14-1.51 (3H, m), 1.52-2.46 (7H, m), 2.78-2.93 and 3.51-3.88 (total 3H, each m), 4.16-4.26 (2H, m), 5.27-5.63 (1H, m), 6.80-8.69 (10H, m).

ESI-MS(m/e): 487 (M+H).

Example 348

1-(2-(6-(6-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-bromo-2-cyano-pyridine, the title compound was obtained as a white solid by the same process as in Example 153, a process based on this or a combination of these with a normal

procedure.

¹H-NMR(CDCl₃) δ : 1.49-2.42 (7H, m), 2.54-2.71 (3H, m), 3.50-3.88 (2H, m), 5.04-5.48 (1H, m), 7.00-8.67 (10H, m).

ESI-MS(m/e): 482 (M+H).

Example 349

3-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-oxo-propionitrile

Using cyanoacetic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.80-2.05 (4H, m), 3.05-3.25 (4H, m), 3.47-3.93 (3H, m), 5.19-5.41 (1H, m), 7.00-7.59 (5H, m), 7.82-7.99 (3H, m), 8.35-8.41 (1H, m), 8.62-8.68 (1H, m).

ESI-MS(m/e): 502 (M+H).

Example 350

Cyclopropyl-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-methanone

Using cyclopropanecarboxylic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.92-1.108 (4H, m), 1.60-1.66 (2H, m), 1.85-1.99 (2H, m), 2.20-2.38 (1H, m), 3.05-3.08 (3H, m), 3.63-4.00 (2H, m), 5.33-5.41 (1H, m), 7.12-7.44 (5H, m), 7.86-7.92 (3H, m), 8.40-8.44 (1H, m), 8.60-8.68 (1H, m).

ESI-MS(m/e): 503 (M+H).

Example 351

3,3,3-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-propan-1-one

Using 3,3,3-trifluoro-propionic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.85-2.40 (4H, m), 2.90-3.27 (5H, m), 3.65-3.90 (2H, m), 5.15-5.43 (1H, m), 6.97-7.63 (5H, m), 7.84-7.96 (3H, m), 8.38-8.43 (1H, m), 8.60-8.68 (1H, m).

ESI-MS(m/e): 545 (M+H).

Example 352

(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-(tetrahydrofuran-2-yl)-methanone

Using tetrahydrofuran-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.85-2.33 (7H, m), 3.05-3.10 (3H, m), 3.63-4.08 (5H, m), 4.15-4.62 (1H, m), 5.33-5.62 (1H, m), 7.11-7.55 (5H, m), 7.84-7.95 (3H, m), 8.37-8.42 (1H, m), 8.60-8.67 (1H, m).

ESI-MS(m/e): 533 (M+H).

Example 353

N-(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-acetamide

Using acetylaminoacetic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.90-2.05 (8H, m), 3.07-3.09 (3H, m), 3.47-4.01 (3H, m), 5.16-5.40 (1H, m), 6.52-6.70 (1H, m), 7.04-7.20 (2H, m), 7.33-7.57 (2H, m), 7.84-7.98 (3H, m), 8.35-8.38 (1H, m), 8.61-8.67 (1H, m).

ESI-MS(m/e): 534 (M+H).

Example 354 (diastereomer A), 355 (diastereomer B)

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer A and diastereomer B

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 1-pyrrolidin-2-yl-ethanol, the title compound was obtained as diastereomer mixture of pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure. The obtained diastereomer mixture was purified further by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1), diastereomer A and B were respectively obtained as pale yellow solid.

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer A.

¹H-NMR(CD₃OD) δ : 1.09 (3H, d, J = 6.7 Hz), 1.66-1.78 (1H, m), 1.80-1.99 (3H, m), 3.06-3.18 (1H, m), 3.12 (3H, s), 3.61-3.69 (1H, m), 3.78-3.83 (1H, m), 3.90-3.99 (1H, m), 6.97-7.81 (5H, m), 7.89-8.00 (3H, m), 8.26 (1H, d, J = 8.2 Hz), 8.74 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 479 (M+H).

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-et

hanol diastereomer B.

¹H-NMR(CD₃OD) δ : 0.76 (3H, d, J = 6.3 Hz), 1.70-1.82 (3H, m), 1.92-2.00 (1H, m), 3.06-3.13 (1H, m), 3.10 (3H, s), 3.61-3.69 (1H, m), 3.83-3.90 (1H, m), 3.95-4.03 (1H, m), 7.04 (2H, d, J = 8.9 Hz), 7.37-7.44 (2H, m), 7.4.6-7.49 (1H, m), 7.89 (2H, d, J = 8.9 Hz), 7.93-7.99 (1H, m), 8.27 (1H, d, J = 7.8). 8.74 (1H, d, J = 4.7 Hz)

ESI-MS(m/e) : 479 [M+H]

Example 3565-(2-(1-fluoro-ethyl)-pyrrolidin-1-yl)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To solution of 1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer A 21mg obtained in Example 354 in chloroform 1 ml was added diethylamino sulphur trifluoride 0.007 ml at -78°C, and the reaction liquor was stirred at 78°C for one hour. The reaction liquor was warmed to room temperature and thereafter, saturated aqueous sodium bicarbonate was added to the reaction liquor and thereafter, it was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as pale yellow solid.

¹H-NMR(CD₃OD) δ : 1.18 and 1.24 (total 3H, each d, J = 6.3, 6.7 Hz), 1.53-1.78 (1H, m), 1.83-2.00 (3H, m), 3.11 (3H, s), 3.11-3.20 (1H, m), 3.52-3.61 (1H, m), 3.89-4.01 (1H, m), 4.63-4.87 (1H, m), 7.04 (2H, d, J = 9.0 Hz), 7.21-7.53 (3H, m), 7.89 (2H, d, J = 9.0 Hz), 7.96-8.02 (1H, m), 8.27 (1H, d, J = 7.8 Hz), 8.74 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 481 (M+H).

Example 3575-(2-(1-fluoro-ethyl)-pyrrolidin-1-yl)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer B obtained in Example 355, the title compound was obtained as a pale yellow solid by the same process as in Example 356, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 0.99 and 1.09 (total 3H, each d, J = 6.5, 6.2 Hz), 1.59-1.83 (3H, m), 1.93-2.03 (1H, m), 3.00-3.10 (1H, m), 3.09 (3H, s), 3.54-3.67 (1H, m), 4.10-4.19 (1H, m), 4.37-4.54 (1H, m), 7.04 (2H, d, J = 8.9 Hz), 7.36-7.48 (3H, m), 7.86 (2H, d, J = 8.9 Hz), 7.94-7.98 (1H, m), 8.25 (1H, d, J = 7.8 Hz), 8.72 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 481 (M+H).

Example 3581-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Oxalyl chloride 0.080 ml and dimethylsulfoxide 0.087 ml were added successively at -78°C to methylene chloride 3 ml, and the reaction liquor was stirred at 78°C for ten minutes, and thereafter, solution of diastereomer mixture of 1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol (obtained in Example 354 and 355) 146 mg in methylene chloride 2 ml was added at -78°C. The reaction liquor was stirred at -78°C for 30 minutes, and thereafter, triethylamine 0.42 ml was added, and the reaction liquor was stirred at -78°C for a further ten minutes, and thereafter, it was warmed to room temperature. Saturated ammonium chloride aqueous solution was added to the reaction liquor, and the mixture was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (Kieselgel™60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as pale yellow solid.

¹H-NMR(CD₃OD) δ : 1.78-2.07 (3H, m), 1.94 (3H, s), 2.20-2.29 (1H, m), 3.06 (3H, s), 3.37-3.45 (1H, m), 3.64-3.77 (1H, m), 4.27-4.30 (1H, m), 6.80-7.44 (5H, m), 7.80-7.88 (3H, m), 8.27-8.40 (1H, m), 8.61-8.62 (1H, m).

ESI-MS(m/e): 477 (M+H).

Example 359 (enantiomer A), 360 (enantiomer B)1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A and enantiomer B**Racemic**

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone (obtained in Example 358) 27 mg was optically resolved on optical resolution column (CHIRALPAK AD-H 2cm φ x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: ethanol, flow rate 10 ml/min), and enantiomer A (retention time = 20.8 min), enantiomer B (retention time = 46.9 min) were respectively obtained as pale yellow solids.

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A.

ESI-MS(m/e): 477 (M+H).

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer B.

ESI-MS(m/e): 477 (M+H).

Example 3611-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 5-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-2-nitro-phenylamine obtained from Example 196 (Step 3) and 1-methyl-1-(2-pyrrolidinyl) ethanol, the title compound was obtained as pale yellow solid by the same process as in Example 354, 355 and 358, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.80-2.10 (3H, m), 2.08 (3H, s), 2.28-2.39 (1H, m), 3.24 (3H, s), 3.40-3.47 (1H, m), 3.66-3.73 (1H, m), 4.46 (1H, t, J = 7.4 Hz), 7.17 (1H, s), 7.40 (1H, s), 7.48 (1H, dd, J = 2.7, 8.8 Hz), 7.54 (1H, dd, J = 4.9, 7.6 Hz), 8.02 (1H, dt, J = 0.8, 7.8 Hz), 8.07 (1H, dd, J = 0.6, 8.8 Hz), 8.24 (1H, d, J = 7.8 Hz), 8.46 (1H, dd, J = 0.6, 2.7 Hz), 7.78 (1H, dt, J = 0.8, 4.9 Hz).

ESI-MS(m/e): 478 (M+H)

Example 362 (enantiomer A), 363 (enantiomer B)1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A and enantiomer B

Racemic 1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone obtained in Example 361 34 mg was optically resolved on optical resolution column (CHIRALPAK AD-H 2cm ϕ x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: ethanol, flow rate 10 ml/min), and enantiomer A (retention time = 28.8 min), enantiomer B (retention time = 48.2 min) were respectively obtained as pale yellow solids.

1-(1-(6-[6-methanesulphonyl-pyridin-3-yloxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A.

ESI-MS(m/e): 478 (M+H).

1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer B

ESI-MS(m/e): 478 (M+H).

Example 364(2S)-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using L-prolinamide hydrochloride and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these

with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.91-2.03 (3H, m), 2.26-2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18-3.28 (1H, m), 3.63-3.91 (1H, m), 4.19-4.23 (1H, m), 6.04-6.13 (1H, m), 6.86-7.28 (4H, m), 7.37-7.41 (1H, m), 7.48-7.54 (1H, m), 7.80-7.92 (3H, m), 8.34-8.38 (1H, m), 8.48-8.63 (1H, m).
ESI-MS(m/e): 478 (M+H).

Example 365

(2R)-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using D-prolinamide and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.91-2.03 (3H, m), 2.26-2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18-3.28 (1H, m), 3.63-3.91 (1H, m), 4.19-4.23 (1H, m), 6.04-6.13 (1H, m), 6.86-7.28 (4H, m), 7.37-7.41 (1H, m), 7.48-7.54 (1H, m), 7.80-7.92 (3H, m), 8.34-8.38 (1H, m), 8.48-8.63 (1H, m).
ESI-MS(m/e): 478 (M+H).

Example 366

6-((3R)-3-fluoro-pyrrolidin-1-yl)-5-(4-methanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using (R)-3-fluoro pyrrolidine and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a yellow oily substance by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.95-2.40 (2H, m), 3.10 (3H, s), 3.25-3.73 (4H, m), 5.14-5.40 (1H, m), 7.06 (2H, d, J = 8.9 Hz), 7.07-7.20 (1H, m), 7.32-7.40 (1H, m), 7.42-7.48 (1H, m), 7.89 (2H, d, J = 8.9 Hz), 7.93-7.99 (1H, m), 8.23 (1H, d, J = 8.2 Hz), 8.71 (1H, d, J = 5.1 Hz)
ESI-MS(m/e): 453 (M+H).

Example 367

1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-3-carboxamide

Using pyrrolidine-3-carboxamide and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 2.03-2.30 (2H, m), 2.89-2.99 (1H, m), 3.06 (3H, s), 3.24-3.60 (4H, m),

5.70-5.86 (2H, m), 7.00-7.48 (5H, m), 7.80-7.90 (3H, m), 8.34-8.40 (1H, m), 8.57-8.64 (1H, m).
ESI-MS(m/e): 478 (M+H).

Example 368

(2R)-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxylic acid methoxy-methyl-amide

Using (R)-N-methoxy-N-methylprolinamide and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.83-2.05 (3H, m), 2.25-2.40 (1H, m), 3.09 (3H, brs), 3.13 (3H, s), 3.40-3.47 (1H, m), 3.68-3.78 (1H, m), 3.84 (3H, brs), 4.90-5.09 (1H, m), 7.06-7.30 (4H, m), 7.42-7.50 (1H, m), 7.87-8.00 (3H, m), 8.19-8.28 (1H, m), 8.70-8.76 (1H, m).

ESI-MS(m/e): 522 (M+H).

Example 369

(2R)-1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(6-ethanesulfonyl-pyridin-3-yloxy)-5-fluoro-2-nitro-phenylamine obtained from Example 221 (Step 2) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as pale yellow solid by the same process as in Example 354, 55 and Example 358, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 1.78-2.03 (3H, m), 2.03 (3H, s), 2.22-2.35 (1H, m), 3.30-3.43 (1H, m), 3.39 (2H, q, J = 7.4 Hz), 3.64-3.75 (1H, m), 4.35-4.42 (1H, m), 7.03-7.48 (4H, m), 7.90-7.99 (1H, m), 8.03 (1H, d, J = 8.6 Hz), 8.17-8.28 (1H, m), 8.43-8.46 (1H, m), 8.70-8.75 (1H, m).

ESI-MS(m/e): 492 (M+H).

Example 370

(2R)-1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(6-ethanesulfonyl-pyridin-3-yloxy)-5-fluoro-2-nitro-phenylamine obtained from Example 225 (Step 2) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as pale yellow solid by the same process as in Example 205 and Example 358, a process based on this or a sequential combination of these with a normal procedure

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 1.80-2.03 (3H, m), 2.04 (3H, s), 2.24-2.34 (1H, m), 3.30-3.45 (1H, m), 3.39 (2H, q, J = 7.4 Hz), 3.63-3.74 (1H, m), 4.37-4.44 (1H, m), 7.07 (1H, brs), 7.22-7.50 (2H, m), 8.03-8.05 (1H, m), 8.42-8.46 (1H, m), 8.63-8.66 (1H, m), 8.73 (1H, d, J

= 1.6 Hz), 9.37-9.43 (1H, m).

ESI-MS(m/e): 493 (M+H).

Example 371

(2R)-1-(1-(6-(4-ethanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(4-ethane sulfonyl-phenoxy)-5-fluoro-2-nitro-phenylamine obtained from Example 259 (Step 1) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 1.81-2.03 (3H, m), 2.02 (3H, s), 2.24-2.33 (1H, m), 3.22 (2H, q, J = 7.4 Hz), 3.38-3.46 (1H, m), 3.72-3.79 (1H, m), 4.40 (1H, t, J = 7.5 Hz), 7.10-7.12 (3H, m), 7.29 (1H, s), 7.45-7.48 (1H, m), 7.87-7.90 (2H, m), 7.90-7.98 (1H, m), 8.24 (1H, d, J = 7.6 Hz), 8.72 (1H, d, J = 4.9 Hz).

ESI-MS(m/e): 491 (M+H).

Example 372

(2R)-1-(1-(6-(4-ethane sulfonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(4-ethane sulfonyl-phenoxy)-5-fluoro-2-nitro-phenylamine obtained from Example 259 (Step 1) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 1.82-2.04 (3H, m), 2.04 (3H, s), 2.24-2.34 (1H, m), 3.22 (2H, q, J = 7.4 Hz), 3.34-3.50 (1H, m), 3.70-3.79 (1H, m), 4.38-4.48 (1H, m), 7.00-7.38 (4H, m), 7.89 (2H, d, J = 9.0 Hz), 8.66 (1H, brs), 8.75 (1H, dd, J = 1.6, 2.5 Hz), 9.38-9.48 (1H, m).

ESI-MS(m/e): 492 (M+H).

Example 373

(2R)-1-(1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-propan-1-one

Using 5-fluoro-4-(6-ethane sulfonyl-pyridin-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 1-(R)-pyrrolidine-2-yl-propanol, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 0.93 (3H, t, J = 7.2 Hz), 1.25-1.27 (3H, m), 1.75-2.00 (3H, m), 2.23-2.53 (3H, m), 3.33-3.44 (3H, m), 3.71 (2H, q, J = 7.3 Hz), 4.43 (1H, t, J = 7.6 Hz), 7.14 (1H, s), 7.38

(1H, s), 7.45-7.50 (2H, m), 7.93-8.00 (1H, m), 8.06 (1H, d, J = 8.8 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.45 (1H, d, J = 2.9 Hz), 8.73 (1H, d, J = 4.9 Hz).

ESI-MS(m/e): 506 (M+H).

Example 374

(2R)-2-(1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-propane-2-ol

Using 5-fluoro-4-(6-ethane sulfonyl-pyridin-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and (R)-1-methyl-1-(2-pyrrolidinyl) ethanol, the title compound was obtained by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 0.85 and 0.87 (total 6H, each s), 1.22 (3H, t, J = 7.3 Hz), 1.59-1.84 (3H, m), 1.93-2.05 (1H, m), 3.08-3.17 (1H, m), 3.31-3.40 (2H, m), 3.53-3.61 (1H, m), 4.00-4.03 (1H, m), 7.43-7.64 (4H, m), 7.91-7.98 (1H, m), 8.02 (1H, d, J = 8.8 Hz), 8.25 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 2.7 Hz), 8.71-8.73 (1H, m).

ESI-MS(m/e): 508 (M+H).

Example 375

(2R, 4R)-4-hydroxy-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using cis-4-hydroxy-D-prolinamide, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.94-2.00 (1H, m), 2.50-2.59 (1H, m), 3.11 (3H, s), 3.38-3.44 (1H, m), 3.73-3.77 (1H, m), 4.23-4.28 (1H, m), 4.36-4.42 (1H, m), 7.12 (2H, d, J = 9.0 Hz), 7.24 (1H, s), 7.33 (1H, s), 7.44-7.47 (1H, m), 7.89-7.97 (3H, m), 8.21-8.24 (1H, m), 8.70-8.72 (1H, m).

ESI-MS(m/e): 494 (M+H).

Example 376

(2R, 4S)-4-fluoro-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using (2R, 4R)-4-hydroxy-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide obtained in Example 375, the title compound was obtained as a pale yellow solid by the same process as in Example 356, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 2.01-2.21 (1H, m), 2.54-2.67 (1H, m), 3.13 (3H, s), 3.48 (1H, dd, J = 12.8, 27.2 Hz), 4.09 (1H, ddd, 3.6, 12.8, 39.7 Hz = J), 4.48 (1H, dd, J = 6.4, 10.0 Hz), 5.20-5.34 (1H, m), 7.15 (2H, d, J = 8.8 Hz), 7.25 (1H, brs), 7.41 (1H, brs), 7.46-7.49 (1H, m), 7.92-7.99 (3H, m),

8.26 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 4.7 Hz).

Example 377

(2R, 4S)-4-hydroxy-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using trans-4-hydroxy-D-prolinamide, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 2.00-2.07 (1H, m), 2.33-2.39 (1H, m), 3.13 (3H, s), 3.25 (1H, d, J = 10.8 Hz), 4.00 (1H, dd, J = 4.1, 10.8 Hz), 4.44-4.50 (2H, m), 7.14 (2H, d, J = 9.0 Hz), 7.23 (1H, brs), 7.37 (1H, brs), 7.46-7.49 (1H, m), 7.92-7.99 (3H, m), 8.25 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 494 (M+H).

Example 378

1-((2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidin-2-yl)-ethanone

Step 1

Synthesis of (2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl-amide

Using (2R, 4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide obtained in Reference Example 5, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

Step 2

Production of 1-((2R,4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidin-2-yl)-ethanone

Methylolithium (1.0M diethyl ether solution) 0.360 ml was added to a solution of 20 mg of the (2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl-amide obtained in step 1 in tetrahydrofuran 1 ml, at -78°C. The reaction liquor was stirred at -78°C for one hour and thereafter, it was warmed to 0°C and was stirred for one hour. Saturated ammonium chloride aqueous solution was added to the reaction liquor, and the mixture was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue obtained was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound as pale yellow solid.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 1.79-1.88 (1H, m), 2.08 (3H, s), 2.43-2.54 (1H, m), 3.33 (2H, q, J = 7.4 Hz), 3.46-3.63 (2H, m), 4.34-4.43 (2H, m), 7.10 (1H, brs), 7.39 (1H, brs), 7.43-7.50 (2H, m), 7.93-7.97 (1H, m), 8.04 (1H, d, J = 8.8 Hz), 8.23 (1H, d, J = 8.0 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.71 (1H, d, J = 4.3 Hz).

ESI-MS(m/e): 508 (M+H).

Example 379

1-((2R, 4S)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrrolidin-2-yl)-ethanone.

Using the 1-((2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidin-2-yl)-ethanone obtained in Example 378, the title compound was obtained as pale yellow solid by the same method as in Example 356, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.31 (3H, t, J = 7.4 Hz), 1.80-2.05 (1H, m), 1.96 and 2.02 (total 3H, each s), 2.26-2.60 (1H, m), 3.30-3.43 (2H, m), 3.43-3.66 (1H, m), 3.70-4.04 (1H, m), 4.50-4.64 (1H, m), 5.12-5.37 (1H, m), 6.90-7.56 (4H, m), 7.80-7.91 (1H, m), 7.93-8.02 (1H, m), 8.30-8.68 (3H, m).

ESI-MS(m/e): 510 (M+H).

Example 380

1-((2R, 4S)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrrolidin-2-yl)-ethanone

Using (2R, 4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide obtained in Reference Example 5, the title compound was obtained as pale yellow solid by the same process as in Example 370 and Example 378 (Step 2) and Example 356, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 1.98-2.20 (1H, m), 2.05 (3H, s), 2.48-2.61 (1H, m), 3.41 (2H, q, J = 7.4 Hz), 3.56 (1H, dd, J = 11.9, 24.5 Hz), 3.99 (1H, ddd, J = 3.1, 11.9, 39.1 Hz), 4.65 (1H, dd, J = 6.6, 10.3 Hz), 5.22-5.36 (1H, m), 7.13 (1H, brs), 7.48-7.50 (2H, m), 8.05 (1H, dd, J = 0.6, 8.8 Hz), 8.52 (1H, d, J = 2.8 Hz), 8.67 (1H, d, J = 2.5 Hz), 8.76 (1H, dd, J = 1.4, 2.5 Hz), 9.43 (1H, d, J = 1.4 Hz)

ESI-MS(m/e): 511 (M+H).

Example 381

5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 2-fluorophenol and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a colourless solid by same process as Example (Step 4)-(Step 6), by a process based on this or a combination of these with a normal

procedure.

¹H-NMR(CD₃OD) δ : 3.10 (3H, s), 6.98-7.05-(1H, m), 7.07-7.21 (5H, m), 7.21-7.66 (3H, m), 7.88 (2H, d, J = 9.0 Hz), 7.98 (1H, t, J = 7.6 Hz), 8.28 (1H, d, J = 8.2 Hz), 8.74 (1H, s).

ESI-MS(m/e): 476 (M+H).

Example 382

5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-(4-methanesulphonyl-phenoxy)-4-(2-fluoro-phenoxy)-benzene-1,2-diamine obtained in Example 381, the title compound was obtained as a brown solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.11 (3H, s), 7.00-7.08 (1H, m), 7.08-7.70 (5H, m), 7.11 (2H, d, J = 8.8 Hz), 7.90 (2H, d, J = 8.8 Hz), 8.71 (1H, s), 8.78 (1H, s), 9.47 (1H, s).

ESI-MS(m/e): 477 (M+H).

Example 383

5-(2,3-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,3-difluoro phenol, the title compound was obtained as pale yellow solid by same process as Example 196, (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 6.79-6.83 (1H, m), 6.98-7.12 (2H, m), 7.17-7.80 (4H, m), 7.98-8.05 (2H, m), 8.27-8.35 (1H, m), 8.39 (1H, d, J = 2.7 Hz), 8.64-8.79 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 384

5-(2,4-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,4-difluoro phenol, the title compound was obtained as pale yellow solid by same process as Example 196 (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.21 (3H, s), 6.91-7.41 (4H, m), 7.47-7.75 (3H, m), 7.98-8.06 (2H, m), 8.27-8.33 (1H, m), 8.40-8.45 (1H, m), 8.66-8.76 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 385

5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,5-difluoro phenol, the title compound was obtained as pale yellow solid by same process

as Example 196 (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 6.85-6.95 (2H, m), 7.24 (1H, td, J = 9.6, 5.1 Hz), 7.53 (1H, s), 7.56 (1H, dd, J = 8.6, 2.7 Hz), 7.64 (1H, dd, J = 7.8, 4.7 Hz), 7.81 (1H, s), 8.05 (1H, d, J = 8.6 Hz), 8.10 (1H, t, J = 7.8 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.43 (1H, d, J = 2.7 Hz), 8.84 (1H, d, J = 4.7 Hz)

ESI-MS(m/e): 495 (M+H).

Example 386

5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,6-difluoro phenol, the title compound was obtained as pale yellow solid by same process as Example 196 (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.22 (3H, s), 7.09-7.17 (2H, m), 7.14 (2H, t, J = 8.2 Hz), 7.26-7.32 (1H, m), 7.47-7.52 (1H, m), 7.55 (1H, dd, J = 9.0, 2.3 Hz), 7.98 (1H, t, J = 7.8 Hz), 8.07 (1H, d, J = 9.0 Hz), 8.27 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.72-8.74 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 387

5-(2,5-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 4-(2,5-difluoro-phenoxy)-5-(6-methanesulphonyl-pyridin-3-yloxy)-benzene-1,2 -diamine obtained in Example 385, the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.21 (3H, s), 6.75-6.92 (2H, m), 7.17-7.24 (1H, m), 7.35-7.85 (2H, m), 7.52 (1H, dd, J = 8.6, 2.7 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.41 (1H, d, J = 2.7 Hz), 8.73 (1H, s), 8.79 (1H, s), 9.50 (1H, s).

ESI-MS(m/e): 496 (M+H).

Example 388

5-(3,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 3,4-difluoro phenol, the title compound was obtained as pale yellow solid by the same process as in Example 383 and Example 387, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CD₃OD) δ : 3.18 (3H, s), 6.65 (1H, brs), 6.80 (1H, brs), 7.17 (1H, q, J = 9.4 Hz), 7.46

(1H, dd, J = 8.6, 2.7 Hz), 7.49-7.80 (2H, m), 8.00 (1H, d, J = 8.6 Hz), 8.33 (1H, d, J = 2.7 Hz), 8.6.9 (1H, s), 8.76 (1H, s), 9.46 (1H, s).

ESI-MS(m/e): 496 (M+H).

Example 389

5-(3,5-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 3,5-difluoro phenol, the title compound was obtained as a pale yellow solid by the same process as in Example 388, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.22 (3H, s), 6.41-6.49 (2H, m), 6.60-6.69 (1H, m), 7.50 (1H, dd, J = 8.6, 2.7 Hz), 7.54-7.82 (2H, m), 8.04 (1H, d, J = 8.6 Hz), 8.36 (1H, d, J = 2.7 Hz), 8.74 (1H, brs), 8.80 (1H, brs), 9.52 (1H, s).

ESI-MS(m/e): 496 (M+H).

Example 390

5-(2-difluoromethoxypyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(5-methyl-pyrazin-2-yl)-1H-benzimidazole

Using 5-methyl-pyrazine-2-carboxylic acid and 4-(2-difluoromethoxy-pyridin-3-yloxy)-5-(6-methanesulphonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 215, the title compound was obtained as a pale yellow solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 2.65 (3H, s), 3.18 (3H, s), 7.15 (1H, dd, J = 8.0, 4.9 Hz), 7.32-7.80 (2H, m), 7.40 (1H, d, J = 7.4 Hz), 7.45 (1H, dd, J = 8.8, 2.7 Hz), 7.46 (1H, t, J = 72.6 Hz), 7.93 (1H, dd, J = 4.9, 1.4 Hz), 8.01 (1H, dd, J = 8.8, 0.6 Hz), 8.35 (1H, dd, J = 2.7, 0.6 Hz), 8.67 (1H, d, J = 1.0 Hz), 9.32 (1H, d, J = 1.3 Hz)

ESI-MS(m/e): 541 (M+H).

Example 391

5-phenoxy-2-pyrazin-2-yl-6-(6-ethane sulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Step 1

Synthesis of pyrazine-2-carboxylic acid (5-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide

Pyrazine-2-carboxylic acid 3.18 g, 1-hydroxybenzotriazole 4.1 g and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 5.8 g were added to a solution of the 3-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-phenylamine obtained in Example 221 (Step 1) 7.5 g dissolved in dimethylformamide 7 ml, the reaction liquor was stirred overnight at room temperature. Water was added to the reaction liquor, and precipitate was

recovered by filtration, to give 8.0g crude product. Fuming nitric acid 0.44 ml was added to a solution of the obtained crude product 3.6g in trifluoroacetic acid 35 ml, and the reaction liquor was stirred at room temperature overnight, and thereafter the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and, precipitate was recovered by filtration, to give the title compound.

Step 2

Production of 5-(2,5-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

2,5-difluoro-phenol 15 mg and cesium carbonate 28 mg were added to a solution of pyrazine-2-carboxylic acid (5-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide obtained in (Step 1) 26 mg in N-methylpyrrolidinone 0.5 ml, and the reaction liquor was stirred at 90°C for 15 minutes, and thereafter, tin (II) chloride dihydrate 100 mg was added to the reaction liquor. The reaction liquor was stirred at 90°C for one hour, and thereafter, ethyl acetate and saturated aqueous sodium bicarbonate were added. The precipitate was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a pale yellow solid.

¹H-NMR(CD₃OD) δ : 1.23 (3H, t, J = 7.2 Hz), 3.24-3.44 (2H, m), 6.82-6.92 (2H, m), 7.04-7.18 (1H, m), 7.26-7.38 (3H, m), 7.48-7.56 (2H, m), 8.03 (1H, d, J = 8.4 Hz), 8.38 (1H, s), 8.74 (1H, s), 8.81 (1H, s), 9.51 (1H, s).

ESI-MS(m/e): 474 (M+H).

Example 392

5-(naphthalen-1-yl

oxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using naphthalene-1-ol and pyrazine-2-carboxylic acid (5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenyl)-amide obtained in Example 391, the title compound was obtained as a brown solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.17 (3H, t, J = 7.4 Hz), 3.29 (2H, q, J = 7.4 Hz), 6.81 (1H, d, J = 7.6 Hz), 7.29-7.40 (3H, m), 7.45-7.49 (1H, m), 7.55 (1H, d, J = 7.6 Hz), 7.56 (1H, s), 7.72 (1H, d, J = 8.6 Hz), 7.75 (1H, s), 7.83 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 8.6 Hz), 8.17 (1H, d, J = 3.0 Hz), 8.70 (1H, dd, J = 2.3, 1.2 Hz), 8.77 (1H, d, J = 2.3 Hz), 9.48 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 524 (M+H).

Example 393

5-(naphthalen-2-yl oxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using naphthalene-2-ol and pyrazine-2-carboxylic acid (5-fluoro-4-(6-ethanesulfonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide obtained in Example 391, the title compound was obtained as a brown solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure..

¹H-NMR(CD₃OD) δ : 1.11 (3H, t, J = 7.6 Hz), 3.24 (2H, q, J = 7.6 Hz), 7.10 (1H, dd, J = 8.8, 2.5 Hz), 7.16 (1H, brs), 7.35-7.46 (3H, m), 7.50 (1H, d, J = 3.1 Hz), 7.52 (1H, d, J = 2.5 Hz), 7.67 (1H, d, J = 8.2 Hz), 7.81 (1H, s), 7.83 (1H, s), 7.95 (1H, d, J = 6.3 Hz), 8.34 (1H, d, J = 2.3 Hz), 8.73 (1H, d, J = 2.7 Hz), 8.80 (1H, dd, J = 2.7, 1.6 Hz), 9.52 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 524 (M+H).

Example 394

5-(2-difluoromethyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-difluoromethyl-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.21 (3H, t, J = 8.4 Hz), 3.37 (2H, q, J = 8.4 Hz), 6.72 (1H, t, J = 59.8 Hz), 6.85-6.90 (1H, m), 7.17 (1H, t, J = 8.6 Hz), 7.39-7.46 (3H, m), 7.51-7.84 (3H, m), 7.98-8.05 (2H, m), 8.31-8.39 (2H, m), 8.65-8.85 (1H, m).

ESI-MS (m/e): 523 (M+H).

Example 395

5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 196, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.3 Hz), 3.37 (2H, q, J = 7.3 Hz), 6.88 (1H, d, J = 8.2 Hz), 7.16 (1H, t, J = 7.4 Hz), 7.40-7.46 (2H, m), 7.51-7.54 (1H, m), 7.64 (1H, brs), 7.70 (1H, brs), 7.87 (1H, d, J = 7.8 Hz), 7.98 (1H, d, J = 8.6 Hz), 8.01 (1H, t, J = 8.6 Hz), 8.30 (1H, d, J = 2.7 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.76 (1H, brs).

ESI-MS (m/e): 516 (M+H).

Example 3965-benzyloxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 4-benzyloxy-3-fluoroaniline obtained in Example 250 (Step 1), picolinic acid and 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained as a brown solid by the same process as in Example 250, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.26 (3H, t, J = 7.6 Hz), 3.35 (2H, q, J = 7.6 Hz), 5.07 (2H, s), 7.10-7.13 (2H, m), 7.15 (1H, s), 7.26-7.27 (4H, m), 7.34-7.39 (1H, m), 7.51 (1Hx1/2, s), 7.64 (1Hx1/2, s), 7.83-7.86 (1H, m), 7.95-7.96 (1H, m), 8.33-8.35 (1H, m), 8.45-8.46 (1H, m), 8.60-8.63 (1H, m), 10.43-10.46 (1H, m).

ESI-MS (m/e): 487 (M+H).

Example 3975-(2-methanesulphonyl-6-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole**Step 1**Synthesis of 5-hydroxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-benzyloxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 396, the title compound was obtained as pale green colored solid by the same process as in Example 251 (Step 1), a process based on this or a combination of these with a normal procedure.

Step 2Production of 5-(2-methanesulphonyl-6-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-hydroxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in (Step 1) and 1,2-difluoro-3-methanesulphonyl-benzene, the title compound was obtained as pale green colored solid by the same process as in Example 251, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 2.97 (3H, s), 3.41 (2H, q, J = 7.4 Hz), 7.11 (1H, s), 7.50-7.57 (2H, m), 7.61-7.70 (2H, m), 7.70 (1H, s), 7.87 (1H, d, J = 8.0 Hz), 7.99 (1H, t, J = 8.0 Hz), 8.10 (1H, d, J = 8.6 Hz), 8.27 (1H, d, J = 7.0 Hz), 8.57 (1H, d, J = 2.7 Hz), 8.74 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 569 (M+H).

Example 3985-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 1,2-difluoro-3-cyano-benzene and 5-hydroxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 397, the title compound was obtained as pale green colored solid by the same process as in Example 251, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.27-7.43 (1H, m), 7.40 (1H, td, J = 8.0, 4.6 Hz), 7.49-7.55 (2H, m), 7.56-7.76 (3H, m), 7.99 (1H, t, J = 7.6 Hz), 8.06 (1H, d, J = 9.0 Hz), 8.30 (1H, d, J = 7.6 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.75 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 516 (M+H).

Example 399

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 397, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD), δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.00-7.18 (1H, m), 7.34-7.43 (2H, m), 7.49 (1H, brs), 7.54-7.56 (2H, m), 7.66 (1H, brs), 7.97 (1H, t, J = 8.0 Hz), 8.07 (1H, d, J = 8.6 Hz), 8.20-8.30 (1H, m), 8.53 (1H, d, J = 2.7 Hz), 8.70-8.77 (1H, m).

ESI-MS (m/e): 534 (M+H).

Example 400

5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

Step 1

Synthesis of 3-fluoro-4-(2-fluoro-6-cyano-phenoxy)-phenylamine

Using (3-fluoro-4-hydroxy-phenyl)-carbamic acid tert-butyl ester obtained in Example 196 (Step 1) and 1,2-difluoro-3-cyano-benzene, the title compound was obtained by the same process as in Example 221 (Step 1), a process based on this or a combination of these with a normal procedure.

Step 2

Synthesis of pyrazine-2-carboxylic acid (5-fluoro-4-(2-fluoro-6-cyano-phenoxy)-2-nitro-phenyl)-amide

Using 5-fluoro-4-(2-fluoro-6-cyano-phenoxy)-phenylamine obtained in (Step 1) and pyrazine-2-carboxylic acid, the title compound was obtained by the same process as in Example 391 (Step 1), a process based on this or a combination of these with a normal procedure.

Step 3

Production of 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H

-benzimidazole

Using pyrazine-2-carboxylic acid (5-fluoro-4-(2-fluoro-6-cyano-phenoxy)-2-nitro-phenyl)- amide obtained in (Step 2) and 4-ethanesulphonyl-phenol, the title compound was obtained as a brown solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.20 (2H, q, J = 7.4 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.33-7.40 (2H, m), 7.55-7.62 (3H, m), 7.86 (2H, d, J = 9.0 Hz), 8.72 (1H, s), 8.78 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 516 (M+H).

Example 4015-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole and 5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole obtained in Example 400, the title compounds were obtained as brown solid and pale yellow solid respectively by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.22 (2H, q, J = 7.4 Hz), 7.00-7.34 (1H, m), 7.23 (2H, d, J = 8.8 Hz), 7.34-7.70 (4H, m), 7.91 (2H, d, J = 8.8 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.46 (1H, s).

ESI-MS (m/e): 534 (M+H).

5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 1.10 (6H, d, J = 9.6 Hz), 1.24 (3H, t, J = 7.4 Hz), 3.01-3.11 (2H, m), 4.06-4.16 (1H, m), 6.80-7.87 (9H, m), 8.52-8.60 (2H, m), 9.51-9.54 (1H, m), 10.78-10.80 (1H, m).

ESI-MS (m/e): 576 (M+H).

Example 4025-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using pyrazine-2-carboxylic acid (5-fluoro-4-(2-cyano-6-fluoro-phenoxy)-2-nitro-phenyl)-amide obtained in Example 400 (Step 2) and 6-ethanesulfonyl-pyridin-3-ol, the title compound was

obtained as a white solid by the same process as in Example 400 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 1.10 (3H, t, J = 7.4 Hz), 3.27-3.36 (2H, m), 7.22-7.35 (1H, m), 7.38-7.50 (2H, m), 7.72-7.77 (3H, m), 7.98 (1H, d, J = 9.0 Hz), 8.50 (1H, d, J = 2.7 Hz), 8.76 (1H, s), 8.79 (1H, s), 9.45 (1H, s).

ESI-MS (m/e): 517 (M+H).

Example 403

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole and
5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin -3-yloxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 402, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

¹H-NMR(CD₃OD) δ : 1.27 (3H, t, J = 7.4 Hz), 3.43 (2H, q, J = 7.4 Hz), 7.08-7.11 (1H, m), 7.38-7.46 (2H, m), 7.46-7.80 (3H, m), 8.10 (1H, d, J = 4.7 Hz), 8.55 (1H, d, J = 2.7 Hz), 8.71 (1H, s), 8.78 (1H, s), 9.47 (1H, s).

ESI-MS (m/e): 535 (M+H).

5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

¹H-NMR(CD₃OD) δ : 1.08 (6H, d, J = 6.6 Hz), 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.94-4.02 (1H, m), 7.10 (1H, s), 7.36-7.46 (3H, m), 7.59 (1H, d, J = 9.0 Hz), 7.74 (1H, s), 8.08 (1H, d, J = 9.0 Hz), 8.56 (1H, s), 8.75 (1H, s), 8.80 (1H, s), 9.44 (1H, s).

ESI-MS (m/e): 577 (M+H).

Example 404

5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin -3-yloxy)-1H-benzimidazole obtained in Example 402, the title compound was obtained as a colourless solid by the same process as in Example 60, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.27 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.37-7.46 (4H, m), 7.60 (1H, s), 7.84 (1H, d, J = 5.9 Hz), 7.94 (1H, d, J = 9.0 Hz), 8.32 (1H, d, J = 2.0 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.47 (1H, s).

ESI-MS (m/e): 560 (M+H).

Example 405

5-(2-methyl sulphanyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-methylsulphanyl-phenol, the title compound was obtained as pale yellow solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.28 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.78 (1H, ddd, J = 7.6, 7.6, 1.5 Hz), 7.03-7.12 (2H, m), 7.08 (1/2H, s), 7.16 (1H, d, J = 7.6 Hz), 7.30 (1H, dd, J = 8.7, 2.5 Hz), 7.36 (1/2H, s), 7.37-7.41 (1H, m), 7.47 (1/2H, s), 7.72 (1/2H, s), 7.86-7.90 (1H, m), 7.97 (1H, d, J = 8.7 Hz), 8.38 (1H, d, J = 2.5 Hz), 8.38-8.41 (1H, m), 8.61-8.63 (1H, m), 11.16 (1/2H, brs), 11.28 (1/2H, brs).

ESI-MS (m/e): 519 (M+H).

Example 406

5-(2-methane sulphinyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole and 5-(2-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

To methanol 3 ml solution of 5-(2-methyl sulphanyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole 46 mg obtained in Example 405 were added water 2 ml and oxone 89 mg, and thereafter the reaction liquor was stirred at room temperature for five hours. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as pale yellow solid.

5-(2-methane sulphinyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 1.30 (3H, t, J = 7.6 Hz), 2.59 (3/2H, s), 2.63 (3/2H, s), 3.38 (2H, q, J = 7.6 Hz), 6.78-6.81 (1H, m), 7.25-7.33 (2H, m), 7.35-7.43 (1H, m), 7.08 (1/2H, s), 7.16 (1H, d, J = 7.6 Hz), 7.30 (1H, dd, J = 8.7, 2.5 Hz), 7.36 (1/2H, s), 7.37-7.41 (1H, m), 7.47 (1/2H, s), 7.72 (1/2H, s), 7.86-7.90 (1H, m), 7.97 (1H, d, J = 8.7 Hz), 8.38 (1H, d, J = 2.5 Hz), 8.38-8.41 (1H, m), 8.61-8.63 (1H, m), 11.16 (1/2H, brs), 11.28 (1/2H, brs).

ESI-MS (m/e): 535 (M+H).

5-(2-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 2.95 (3/2H, s), 3.02 (3/2H, s), 3.36 (2H, q, J = 7.4 Hz), 6.92-6.97 (1H, d), 7.20-7.27 (1H, m), 7.31-7.35 (3/2H, m), 7.41-7.45 (3/2H, m), 7.51-7.57 (1H, m), 7.65 (1/2H, s), 7.72 (1/2H, s), 7.87-7.92 (1H, m), 7.97-8.04 (2H, m), 8.34-8.42 (2H, m), 8.65-8.67 (1H, m), 10.72 (1H, brs).

ESI-MS (m/e): 551 (M+H).

Example 407

5-(2-bromopyridin-3-yloxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-bromo-pyridin-3-ol and pyrazine-2-carboxylic acid (5-fluoro-4-(6-ethanesulfonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide obtained in Example 391, the title compound was obtained as pale yellow solid by the same process as in Example 391, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.30 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.03 (1H, dd, J = 8.0, 1.6 Hz), 7.19-7.22 (1H, m), 7.28-7.32 (1H, m), 7.34 (1/2H, brs), 7.51 (1/2H, brs), 7.62 (1/2H, brs), 7.93 (1/2H, brs), 8.00 (1H, d, J = 8.6 Hz), 8.14 (1H, brs), 8.31-8.32 (1H, m), 8.62 (1H, brs), 8.70 (1H, d, J = 2.4 Hz), 9.64 (1H, brs), 10.91 (1/2H, brs), 10.98 (1/2H, brs).

ESI-MS (m/e): 553 (M+H).

Example 408

5-(2-vinylpyridin-3-yloxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-vinyl-pyridin-3-ol, the title compound was obtained as a pale yellow solid by the same process as in Example 407, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.27 (3H, t, J = 7.5 Hz), 3.37 (2H, q, J = 7.5 Hz), 5.34 (1H, dd, J = 10.9, 1.9 Hz), 6.30 (1H, dd, J = 17.4, 1.9 Hz), 6.72 (1H, dd, J = 17.4, 10.9 Hz), 7.09 (1H, dd, J = 8.2, 1.5 Hz), 7.12 (1H, dd, J = 8.2, 4.3 Hz), 7.27 (1H, dd, J = 8.7, 2.9 Hz), 8.00 (1H, d, J = 8.7 Hz), 8.31 (1H, d, J = 2.9 Hz), 8.33 (1H, dd, J = 4.3, 1.5 Hz), 8.61 (1H, dd, J = 2.6, 1-6 Hz), 8.69 (1H, d, J = 2.6 Hz), 10.60 (1/2H, brs), 10.68 (1/2H, brs).

ESI-MS (m/e): 501 (M+H).

Example 409

5-(2-cyclopropylpyridin-3-yloxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

midazole

Using 2-cyclopropyl-pyridin-3-ol, the title compound was obtained as a pale yellow solid by the same process as in Example 407, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.77-1.02 (2H, m), 1.24-1.31 (2H, m), 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 6.96 (2/5H, dd, J = 8.2, 4.6 Hz), 6.98 (3/5H, dd, J = 8.2, 4.6 Hz), 7.03 (2/5H, dd, J = 8.2, 1.5 Hz), 7.04 (3/5H, dd, J = 8.2, 1.5 Hz), 7.16 (1/2H, s), 7.33 (1H, dd, J = 8.8, 3.0 Hz), 7.48 (1/2H, s), 7.53 (1/2H, s), 7.78 (1/2H, s), 8.00 (1H, d, J = 8.8 Hz), 8.20 (2/5H, dd, J = 4.6, 1-5 Hz), 8.22 (3/5H, dd, J = 4.6, 1.5 Hz), 8.39 (2/5H, d, J = 3.0 Hz), 8.40 (3/5H, d, J = 3.0 Hz), 8.59-8.62 (1H, m), 8.68-8.70 (1H, m), 9.62-9.64 (1H, m), 10.60 (3/5H, brs), 10.66 (2/5H, brs).

ESI-MS (m/e): 515 (M+H).

Example 4105-(2-difluoromethoxypyridin-3-yloxy)-2-pyridin-2-yl-6-(4-dimethylsulphamoyl-phenoxy)-1H-benzimidazole

4-(N,N-dimethylamino sulfonyl)-phenol and 2-difluoromethoxy-pyridin-3-ol were successively used, and, by the same process as in Example 221 (Step 1)-(Step 3), a process based on these or a combination of these with a normal procedure, the title compound was obtained as pale yellow solid.

¹H-NMR(CD₃OD) δ : 2.66 (6H, s), 7.05 (2H, d, J = 8.6 Hz), 7.10-7.19 (1H, m), 7.32-7.62 (4H, m), 7.49 (1H, t, J = 72.8 Hz), 7.71 (2H, d, J = 8.6 Hz), 7.91 (1H, d, J = 4.1 Hz), 8.01 (1H, t, J = 7.8 Hz), 8.32 (1H, d, J = 7.6 Hz), 8.77 (1H, s).

ESI-MS (m/e): 554 (M+H).

Example 4115-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

4-methanesulphonyl-3-chloro-phenol and 2-difluoromethoxy-pyridin-3-ol were successively used, and, by the same process as in Example 221 (Step 1)-(Step 3), a process based on these or a combination of these with a normal procedure, the title compound was obtained as pale yellow solid.

¹H-NMR(CD₃OD) δ : 3.25 (3H, s), 6.98 (1H, dd, J = 8.6, 2.3 Hz), 7.09 (1H, d, J = 2.3 Hz), 7.15 (1H, dd, J = 7.8, 4.9 Hz), 7.35-7.46 (2H, m), 7.46-7.74 (3H, m), 7.48 (1H, t, J = 74.0 Hz), 7.91-7.94 (1H, m), 8.02 (1H, d, J = 8.6 Hz), 8.32 (1H, d, J = 7.8 Hz), 8.75-8.77 (1H, m).

ESI-MS (m/e): 552 (M-H).

Example 4125-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-(N-hydroxycarbamimidoyl)-phenoxy)-1H-

benzimidazole

To ethanol 0.5 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-cyano-pyridin-3-yloxy)-1H-benzimidazole 6.0 mg obtained in Example 252 was added hydroxyamine (50 % aqueous solution) 0.5 ml, and the reaction liquor was stirred at room temperature for three hours. Thereafter the title compound was obtained as pale yellow solid by eliminating the solvent under reduced pressure.

¹H-NMR(CD₃OD) δ : 7.01-7.04 (1H, m), 7.10-7.22 (3H, m), 7.29-7.35 (2H, m), 7.60 (1H, s), 7.82 (1H, d, J = 9.0 Hz), 8.24 (1H, d, J = 2.3 Hz), 8.70 (1H, d, J = 1.6 Hz), 8.77 (1H, d, J = 1.6 Hz), 9.48 (1H, s).

ESI-MS (m/e): 458 (M+H).

Example 4135-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-(5-methyl-[1,2,4]oxadiazole)-3-yloxy)-1H-benzimidazole

Acetic anhydride 1 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-(N-hydroxycarbamimidoyl)-phenoxy)-1H-benzimidazole 3.6 mg obtained in Example 412 was stirred overnight at 60°C. The solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a colourless solid.

¹H-NMR(CD₃OD) δ : 2.69 (3H, s), 7.00-7.40 (5H, m), 7.48 (1H, dd, J = 7.8, 2.3 Hz), 7.52-7.85 (1H, m), 8.10 (1H, d, J = 7.8 Hz), 8.37 (1H, d, J = 2.3 Hz), 8.71 (1H, s), 8.78 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 482 (M+H).

Example 4145-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-(5-trifluoromethyl-[1,2,4]oxadiazole)-3-yloxy)-1H-benzimidazole

Anhydrous trifluoroacetic acid 1 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-(N-hydroxycarbamimidoyl)-phenoxy)-1H-benzimidazole 2.0 mg obtained in Example 412 was stirred at 60°C for one hour. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 15/1), and the title compound was obtained as a colourless solid.

¹H-NMR(CD₃OD) δ : 7.00-7.50 (5H, m), 7.55 (1H, dd, J = 7.8 Hz, 2.3 Hz), 7.60-7.80 (1H, m),

8.22 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 2.3 Hz), 8.73 (1H, s), 8.80 (1H, s), 9.50 (1H, s).

ESI-MS (m/e): 536 (M+H).

Example 415

5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(imidazo [1,2-a] pyridine-6-yloxy)-1H -benzimidazole

Step 1

Synthesis of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-nitro-pyridin-3-yloxy)-1H -benzimidazole

Using 2-nitro-5-pyridine, the title compound was obtained by the same process as in Example 251 (Step 2), a process based on these or a combination of these with a normal procedure.

Step 2

Production of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(imidazo [1,2-a] pyridine-6-yloxy) -1H-benzimidazole

To methanol 0.5 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-nitro-pyridin-3-yloxy)-1H-benzimidazole 12 mg obtained in (Step 1), expanded Raney nickel catalyst was added, and the reaction liquor was stirred under a hydrogen atmosphere for one hour. The catalyst was eliminated by filtration, and next the solvent was eliminated by distillation under reduced pressure. To ethanol 0.3 ml solution of the obtained residue, chloroacetaldehyde (40 % aqueous solution) 0.02 ml was added, and thereafter the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, then the residue was purified by preparative thin layer chromatography (Kieselgel TM60F254, Art5744 (Merck Co.), chloroform/methanol = 15/1) and the title compound was obtained as pale yellow solid.

¹H-NMR (CDCl₃) δ : 1.25 (3H, t, J = 7.0 Hz), 3.73 (2H, q, J = 7.0 Hz), 7.00-7.22 (6H, m), 7.31-7.65 (4H, m), 7.82 (1/2H, s), 7.88 (1/2H, s), 8.57 (1H, dd, J = 2.5, 1.5 Hz), 8.64 (1H, s), 9.59 (1H, s), 10.57 (1/2H, brs), 10.97 (1/2H, brs).

ESI-MS (m/e): 439 (M+H).

Example 416

5-(pyridin-2-yl sulphanyl)-2-pyrazin-2-yl-6 -(6-ethanesulfonyl-pyridin- 3-yloxy)-1H-benzimidazole

Using pyridine-2-thiol, the title compound was obtained as yellow solid by the same process as in Example 391 (Step 1), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.23 (3H, t, J = 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 7.07 (1H, d, J = 8.2 Hz), 7.11 (1H, dd, J = 7.4, 4.9 Hz), 7.41 (1H, d, J = 7.6 Hz), 7.58-7.80 (1H, m), 7.60 (1H, td, J = 7.6, 1.8 Hz), 7.95 (1H, dd, J = 8.6, 0.6 Hz), 8.00-8.25 (1H, m), 8.28 (1H, dd, J = 5.1, 1.0 Hz), 8.33 (1H, d, J = 0.6 Hz), 8.75 (1H, d, J = 2.5 Hz), 8.82 (1H, dd, J = 2.5, 1.5 Hz), 9.53 (1H, d, J = 1.5 Hz).

ESI-MS (m/e): 491 (M+H).

Example 4175-(3-cyano-pyridin-2-ylsulphanyl)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 3-cyano-pyridine-2-thiol, the title compound was obtained as yellow solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J = 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 7.08 (1H, dd, J = 7.8, 4.9 Hz), 7.35 (1H, dd, J = 8.6, 2.8 Hz), 7.35 and 7.65 (total 1H, each s), 7.80 (1H, dd, J = 7.8, 1.8 Hz), 7.93 (1H, d, J = 8.4 Hz), 7.95 and 8.22 (total 1H, each s), 8.36 (2H, d, J = 2.5 Hz), 8.63 (1H, s), 8.71 (1H, s), 9.65 (1H, d, J = 1.4 Hz).

ESI-MS (m/e): 516 (M+H).

Example 4185-(2-chlorophenyl-sulphanyl)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-chloro-thiophenol, the title compound was obtained as pale yellow solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.20 (3H, s), 7.03-7.10 (1H, m), 7.13-7.20 (2H, m), 7.34-7.39 (2H, m), 7.50-7.86 (3H, m), 7.94 (1H, d, J = 8.6 Hz), 8.01 (1H, t, J = 7.8 Hz), 8.29-8.35 (2H, m), 8.77 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 509 (M+H).

Example 4194-(2-cyano-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2-cyano-phenol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.78 (1H, s), 7.12 (1H, d, J = 8.6 Hz), 7.29-7.31 (2H, m), 7.50-7.51 (1H, m), 7.63-7.65 (2H, m), 7.82 (1H, d, J = 7.4 Hz), 7.9-5-7.97 (1H, m), 8.08 (1H, d, J = 8.6 Hz), 8.32 (1H, d, J = 8.2 Hz), 8.55 (1H, d, J = 2.7 Hz), 8.75 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 498 (M+H).

Example 4204-(2-cyano-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-cyano-phenoxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 419, the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.27 (3H, t, J = 8.0 Hz), 3.42 (2H, q, J = 8.0 Hz), 6.79-6.84 (1H, m), 7.14-7.17 (1H, m), 7.31-7.35 (1H, m), 7.61-7.68 (2H, m), 7.80-7.85 (2H, m), 8.08 (1H, d, J = 8.4 Hz), 8.54-8.59 (1H, m), 8.70-8.73 (1H, m), 8.77-8.79 (1H, m), 9.48-9.50 (1H, m).

ESI-MS (m/e): 499 (M+H).

Example 421

4-(2-cyano-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 286, the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.24 (3H, s), 6.80-6.83 (1H, m), 7.72 (1, H, q, J = 8.6 Hz), 7.30-7.50 (2H, m), 7.60-7.80 (2H, m), 7.88 (1H, d, J = 7.8 Hz), 8.11 (1H, d, J = 9.0 Hz), 8.56 (1H, s), 8.73 (1H, s), 8.79 (1H, s), 9.50 (1H, 1).

ESI-MS (m/e): 485 (M+H).

Example 422

4-(2,3-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2,3-difluoro-phenol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 3.23 (3H, s), 6.70 (1H, d, J = 2.3 Hz), 7.12-7.25 (3H, m), 7.29 (1H, d, J = 2.3 Hz), 7.60-7.65 (2H, m), 8.07-8.10 (2H, m), 8.39 (1H, d, J = 7.9 Hz), 8.50 (1H, d, J = 3.4 Hz), 8.83-8.85 (1H, m).

ESI-MS (m/e): 495 (M+H).

Example 423

4-(2,3-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 3-(2,3-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 285, the title compound was obtained by the same process as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.6 Hz), 3.40 (2H, q, J = 7.-6 Hz), 6.71 (1H, d, J = 2.0 Hz), 7.12-7.26 (3H, m), 7.30 (1H, d, J = 2.0 Hz), 7.60-7.68 (2H, m), 8.06-8.13 (2H, m), 8.40 (1H,

d, J = 7.4 Hz), 8.52 (1H, d, J = 2.7 Hz), 8.86 (1H, d, J = 5.1 Hz).

ESI-MS (m/e): 509 (M+H).

Example 424

4-(2,5-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

2,5-difluoro-phenol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 8.2 Hz), 3.41 (2H, q, J = 8.2 Hz), 6.59 (1H, s), 6.99-7.05 (1H, m), 7.06-7.14 (1H, m), 7.22 (1H, br, s), 7.34 (1H, td, J = 9.8, 4.9 Hz), 7.61 (1H, dd, J = 8.6, 4.3 Hz), 8.07 (1H, d, J = 8.6 Hz), 8.52, (1H, d, J = 4.3 Hz), 8.72 (1H, d, J = 1.2 Hz), 8.79 (1H, s), 9.54 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 510 (M+H).

Example 425

4-(2,5-difluoro-phenoxy)-6-(6-ethansulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2,5-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 424, the title compound was obtained as a white solid by the same process as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.5 Hz), 3.40 (2H, q, J = 7.5 Hz), 6.55 (1H, s), 6.96-7.05 (1H, m), 7.05-7.14 (1H, m), 7.21 (1H, s), 7.28-7.38 (1H, m), 7.50-7.56 (1H, m), 7.56-7.63 (1H, m), 7.97-8.03 (1H, m), 8.07 (1H, d, J = 8.2 Hz), 8.38 (1H, d, J = 7.0 Hz), 8.51 (1H, s), 8.76 (1H, s).

ESI-MS (m/e): 509 (M+H).

Example 426

4-(2,6-difluoro-phenoxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 4-ethansulphonyl phenol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 6.37 (1H, brs), 7.13-7.25 (5H, m), 7.34-7.39 (1H, m), 7.89 (2H, d, J = 8.8 Hz), 8.78 (1H, d, J = 2.7 Hz), 8.84 (1H, dd, J = 1.6, 2.7 Hz), 9.56 (1H, d, J = 1.6 Hz)

ESI-MS (m/e): 509 (M+H).

Example 427

4-(2,6-difluoro-phenoxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 426, the title compound was obtained by the same process as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 6.23 (1H, brs), 7.08 (1H, brs), 7.15-7.22 (4H, m), 7.28-7.38 (1H, m), 7.51 (1H, t, J = 5.9 Hz), 7.87 (2H, d, J = 9.0 Hz), 8.00 (1H, t, J = 7.4 Hz), 8.41 (1H, d, J = 7.4 Hz), 8.76 (1H, brs).

ESI-MS (m/e): 508 (M+H).

Example 4284-(2-difluoromethyl-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2-difluoromethyl-phenol and 6-ethanesulfonyl-pyridin-3-ol were used successively and the title compound was obtained as a colourless solid by the same process as in Example 274, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.50 (1H, s), 7.15 (1H, d, J = 7.4 Hz), 7.22 (1H, t, J = 55.5 Hz), 7.34 (1H, t, J = 7.4 Hz), 7.49-7.62 (4H, m), 7.74 (1H, d, J = 7.4 Hz), 7.98 (1H, t, J = 7.4 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.37 (1H, d, J = 7.4 Hz), 8.49 (1H, d, J = 2.3 Hz), 8.74-8.77 (1H, m).

ESI-MS (m/e): 523 (M+H).

Example 4294-(2-difluoromethyl-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-difluoromethyl-phenoxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene -1,2-diamine obtained in Example 428, the title compound was obtained as yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.8 Hz), 3.40 (2H, q, J = 7.8 Hz), 6.54 (1H, s), 7.17 (1H, d, J = 7.4 Hz), 7.21 (1H, t, J = 55.8 Hz), 7.36 (1H, t, J = 7.4 Hz), 7.50-7.65 (2H, m), 7.75 (1H, d, J = 7.4 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.72 (1H, s), 8.79 (1H, s), 9.54 (1H, s).

ESI-MS (m/e): 524 (M+H).

Example 4304-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

2-difluoromethoxy-pyridin-3-ol and 4-ethansulphonyl-phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.3 Hz), 3.40 (2H, q, J = 7.3 Hz), 6.60 (1H, d, J = 2.0 Hz), 7.27-7.30 (2H, m), 7.57-7.61 (2H, m), 7.64 (1H, t, J = 72.1 Hz), 7.73 (1H, dd, J = 7.8, 1.6 Hz), 8.05-8.08 (2H, m), 8.10 (1H, dd, J = 4.9, 1.6 Hz), 8.37 (1H, d, J = 8.2 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.81 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 540 (M+H).

Example 431

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole

Using

3-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 274 (Step 1), the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 3.65 (3H, s), 6.38 (1H, t, J = 7.2 Hz), 6.44 (1H, s), 7.07 (1H, s), 7.15-7.22 (2H, m), 7.40 (1H, d, J = 7.0 Hz), 7.57 (1H, dd, J = 7.0, 1.8 Hz), 7.84-7.90 (2H, m), 8.70 (1H, s), 8.76 (1H, s), 9.52 (1H, s).

ESI-MS (m/e): 504 (M+H).

Example 432

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

1-methyl-2-oxo-1,2-dihydro-pyridin-3-ol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.65 (5H, s), 6.36 (1H, t, J = 6.7 Hz), 6.46 (1H, s), 7.13 (1H, s), 7.38-7.60 (4H, m), 7.95-8.08 (2H, m), 8.35 (1H, s), 8.49 (1H, s), 8.73 (1H, s).

ESI-MS (m/e): 504 (M+H).

Example 433

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 432, the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 1.13 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.50 (3H, s), 6.24 (1H,

t, J = 6-8 Hz), 6.46 (1H, s), 7.05 (1H, brs), 7.32-7.40 (1H, m), 7.58 (1H, dd, J = 8.8, 2.5 Hz), 7.74 (1H, dd, J = 6.8, 2.0 Hz), 8.01 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 2.5 Hz), 8.79 (1H, d, J = 2.2 Hz), 8.82 (1H, dd, J = 2.5, 1.5 Hz), 9.47 (1H, d, J = 1.4 Hz).

ESI-MS (m/e): 505 (M+H).

Example 434

4-(2-cyano-pyridin-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Step 1

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(1-oxy-pyridin-3-yloxy)-phenylamine

Using 1-oxy-pyridin-3-ol and 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 67 (Step 1) and (Step 2), a process based on these or a combination of these with a normal procedure and this.

Step 2

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(2-cyano-pyridin-3-yloxy)-phenylamine

Using 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(1-oxy-pyridin-3-yloxy)-phenylamine, the title compound was obtained by the same process as in Example 218 (Step 2), a process based on this or a combination of these with a normal procedure.

Step 3

Production of 4-(2-cyano-pyridin-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(2-cyano-pyridin-3-yloxy)-phenylamine, the title compound was obtained by the same process as in Example 196 (Step 5) and 204 (Step 1), a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.23 (3H, s), 7.07 (1H, brs), 7.44 (1H, brs), 7.56-7.69 (4H, m), 8.02 (1H, t, J = 7.8 Hz), 8.09 (1H, d, J = 8.6 Hz), 8.29 (1H, d, J = 7.8 Hz), 8.46-8.48 (1H, m), 8.55-8.57 (1H, m), 8.78-8.80 (1H, m).

ESI-MS (m/e): 485 (M+H).

Example 435

4-(2-cyano-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-ethanesulphonyl-phenol, the title compound was obtained by the same process as in Example 434, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.3 Hz), 3.22 (2H, q, J = 7.3 Hz), 6.94 (1H, brs), 7.27 (2H, d, J = 8.6 Hz), 7.33 (1H, brs), 7.49 (2H, d, J = 8.6 Hz), 7.59-7.62 (1H, m), 7.91-7.98 (3H, m), 8.24 (1H, d, J = 8.6 Hz), 8.45 (1H, d, J = 5.1 Hz), 8.74 (1H, d, J = 5.5 Hz)

ESI-MS (m/e): 498 (M+H).

Example 4364-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Benzyl alcohol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.6 Hz), 3.45 (2H, q, J = 7.6 Hz), 5.41 (2H, s), 7.02-7.05 (1H, m), 7.15-7.17 (1H, m), 7.39-7.45 (3H, m), 7.53-7.59 (4H, m), 8.07 (1H, d, J = 8.6 Hz), 8.11-8.14 (1H, m), 8.39 (1H, d, J = 7.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.87-8.90 (1H, m).

ESI-MS (m/e): 487 (M+H).

Example 4374-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-benzyloxy-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 436, the title compound was obtained by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.27 (3H, t, J = 7.4 Hz), 3.42 (2H, q, J = 7.4 Hz), 5.38 (2H, s), 6.80 (1H, d, J = 2.0 Hz), 7.06 (1H, d, J = 2.0 Hz), 7.36-7.42 (3H, m), 7.49 (1H, dd, J = 8.8, 2.9 Hz), 7.54 (2H, d, J = 6.7 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.7 Hz), 8.78-8.80 (1H, m), 9.54-9.56 (1H, m).

ESI-MS (m/e): 488 (M+H).

Example 4384-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole**Step 1**Synthesis of 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 436, the title compound was obtained by the same process as in Example 251 (Step 1), by a process based on this or a combination of these with a normal procedure.

Step 2Production of 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole and 2,3-difluoro benzonitrile, the title compound was obtained by the same process as in Example 251 (Step 2), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.61 (1H, d, J = 2.0 Hz), 7.28 (1H, d, J = 2.0 Hz), 7.36-7.42 (1H, m), 7.48-7.54 (1H, m), 7.58-7.63 (2H, m), 7.65-7.69 (1H, m), 8.07 (2H, d, J = 8.2 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.82 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 516 (M+H).

Example 439

4-(6-cyano-pyridin-2-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 438 (Step 1) and 2-chloro-3-cyanopyridine, the title compound was obtained by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.42 (2H, q, J = 7.4 Hz), 7.21 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 7.4, 5.1 Hz), 7.48 (1H, d, J = 2.0 Hz), 7.58 (1H, dd, J = 5.1, 7.8 Hz), 7.71 (1H, dd, J = 8.8, 2.9 Hz), 8.00-8.05 (1H, m), 8.11 (1H, d, J = 8.6 Hz), 8.26-8.33 (3H, m), 8.60 (1H, d, J = 2.7 Hz), 8.78 (1H, d, J = 5.1 Hz).

ESI-MS (m/e): 499 (M+H).

Example 440

4-(2-cyano-3-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 2,6-difluoro benzonitrile, the title compound was obtained by the same process as in Example 439, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.91 (1H, d, J = 8.6 Hz), 7.04 (1H, d, J = 1.8 Hz), 7.13 (1H, t, J = 8.6 Hz), 7.44 (1H, d, J = 1.8 Hz), 7.55-7.64 (2H, m), 7.67 (1H, dd, J = 8.6, 3.2 Hz), 8.00-8.06 (1H, m), 8.10 (1H, d, J = 8.6 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.57 (1H, d, J = 2.3 Hz), 8.78-8.81 (1H, m).

ESI-MS (m/e): 516 (M+H).

Example 441

4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 438, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.53 (1H, brs), 7.26 (1H, brs), 7.42-7.53 (2H, m), 7.57-7.62 (2H, m), 7.68 (1H, dd, J = 8.2, 3.9 Hz), 8.07 (1H, d, J = 8.6

Hz), 8.11-8.16 (1H, m), 8.41 (1H, d, J = 8.2 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.88 (1H, d, J = 3.9 Hz)

ESI-MS (m/e): 534 (M+H).

Example 442

4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 437, the title compound was obtained by the same process as in Example 438, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.57 (1H, brs), 7.23 (1H, brs), 7.46-7.51 (1H, m), 7.57-7.61 (1H, m), 7.64-7.71 (2H, m), 8.06 (1H, d, J = 9.0 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.78 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 517 (M+H).

Example 443

4-(2-cyano-5-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2,4-difluoro-benzonitrile and 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 442, the title compound was obtained by same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.20 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.88 (1H, d, J = 10.2 Hz), 6.98 (1H, d, J = 2.0 Hz), 7.05-7.11 (1H, m), 7.39-7.44 (1H, m), 7.68 (1H, dd, J = 3.1, 8.0 Hz), 7.89 (1H, dd, J = 8.8, 6, 1Hz), 8.08-8.12 (1H, m), 8.57-8.60 (1H, m), 8.71 (1H, d, J = 2.3 Hz), 8.77-8.79 (1H, m), 9.46-9.48 (1H, m).

ESI-MS (m/e): 517 (M+H).

Example 444

4-(2-cyano-4-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2,5-difluoro benzonitrile, the title compound was obtained by the same process as in Example 443, by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.81 (1H, d, J = 2.3 Hz), 7.22 (1H, dd, J = 4.6, 9.0 Hz), 7.35 (1H, d, J = 2-3 Hz), 7.45 (1H, ddd, J = 8.6, 4.6, 7.4 Hz), 7.63-7.69 (2H, m), 7.72-7.75 (1H, m), 8.09 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 3.1 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79 (1H, dd, J = 2.0, 3.1 Hz), 9.49 (1H, d, J = 2.0 Hz).

ESI-MS (m/e): 517 (M+H).

Example 445**4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole**

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 442, the title compound was obtained by same process as in Example 43, by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.39 (1H, s), 7.21 (1H, s), 7.42-7.51 (2H, m), 7.55 (1H, dd, J = 8.6, 2.7 Hz), 7.64 (1H, d, J = 7.4 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.75-8.78 (1H, m), 8.82-8.84 (1H, m), 9.54 (1H, brs).

ESI-MS (m/e): 535 (M+H).

Example 446**4-(6-cyano-pyridin-2-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole**

Using 2-chloro-3-cyanopyridine, the title compound was obtained by the same process as in Example 443, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 7.14 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 7.4, 5.1 Hz), 7.45 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 9.0, 2.7 Hz), 8.10 (1H, d, J = 9.0 Hz), 8.27-8.33 (2H, m), 8.59 (1H, d, J = 2.7 Hz), 8.70-8.72 (1H, m), 8.76-8.79 (1H, m), 9.41-9.43 (1H, 1).

ESI-MS (m/e): 500 (M+H).

Example 447**4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained as a pale yellow solid by the same process as in Example 438, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.23 (3H, s), 6.50 (1H, s), 7.22/(1H, s), 7.45-7.62 (3H, m), 7.62-7.78 (2H, m), 7.95-8.05 (1H, m), 8.08 (1H, d, J = 8.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.49 (1H, s), 8.77 (1H, s).

ESI-MS (m/e): 502 (M+H).

Example 448**4-(2-fluoro-6-methanesulphonyl-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 2,3-difluoro-methanesulphonyl benzene and 4-hydroxy-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 447, the title compound was

obtained by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.21 (3H, s), 3.46 (3H, s), 6.54 (1H, d, J = 2.0 Hz), 7.27 (1H, d, J = 2.0 Hz), 7.54-7.67 (3H, m), 7.70-7.74 (1H, m), 7.93 (1H, d, J = 7.8 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.11 (1H, ddd, J = 7.8, 8.6, 2.7 Hz), 8.40 (1H, d, J = 7.8 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.86 (1H, d, J = 5.1 Hz).

ESI-MS (m/e): 555 (M+H).

Example 449

4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 447, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.22 (3H, s), 6.53 (1H, d, J = 1.6 Hz), 7.25 (1H, d, J = 1.6 Hz), 7.42-7.53 (2H, m), 7.57 (1H, dd, J = 8.6, 2.7 Hz), 7.61 (1H, d, J = 7.4 Hz), 7.68 (1H, dd, J = 7.6, 14.3 Hz), 8.06 (1H, d, J = 9.0 Hz), 8.10-8.16 (1H, m), 8.41 (1H, d, J = 8.2 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.8.7 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 520 (M+H).

Example 450

4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 442, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 3.23 (3H, s), 6.57 (1H, brs), 7.23 (1H, brs), 7.49 (1H, td, J = 8.0, 4.6 Hz), 7.59 (1H, dd, J = 9.0, 3.2 Hz), 7.65-7.71 (2H, m), 8.07 (1H, d, J = 9.0 Hz), 8.50 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.78 (1H, brs), 9.48 (1H, brs).

ESI-MS (m/e): 503 (M+H).

Example 451

4-(pyridin-2-ylsulphonyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained as pale-brown solid by the same process as in Example 288, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.31 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.03 (1H, d, J = 8.0 Hz),

7.08 (1H, ddd, J = 7.4, 4.7, 1.0 Hz), 7.35 (1H, d, J = 2.2 Hz), 7.38-7.44 (2H, m), 7.52 (1H, td, J = 7.8, 2.0 Hz), 7.64 (1H, d, J = 2.1 Hz), 7.88 (1H, td, J = 7.8, 1.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.45 (1H, dd, J = 4.9, 1.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.64 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 490 (M+H).

Example 452

4-(pyridin-2-yl

sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(pyridin-2-yl sulphanyl)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 451, the title compound was obtained as yellow solid by the same method as in-Example 68, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.32 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.08-7.19 (2H, m), 7.38 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.6, 2.8 Hz), 7.57 (1H, td, J = 7.8, 1.8 Hz), 7.66 (1H, d, J = 2.2 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 4.7 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.63 (1H, t, J = 2.0 Hz), 8.69 (1H, d, J = 2.5 Hz), 9.63 (1H, d, J = 1.4 Hz)

ESI-MS (m/e): 491 (M+H).

Example 453

4-(1-methyl-1H-imidazol-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 1-methyl-1H-imidazole-2-thiol, the title compound was obtained as yellow solid by the same process as in Example 452, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.33 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 3.94 (3H, s), 6.65-6.69 (1H, m), 6.77 (1H, d, J = 1.4 Hz), 6.87 (1H, d, J = 1.6 Hz), 7.23 (1H, d, J = 2.4 Hz), 7.48 (1H, dd, J = 8.6, 2.8 Hz), 7.72 (1H, d, J = 2.2 Hz), 8.05 (1H, dd, J = 8.6, 0.6 Hz), 8.16 (1H, d, J = 2.6 Hz), 8.54 (1H, dd, J = 2.8, 0.6 Hz), 9.42 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 494 (M+H).

Example 454

4-(4-methoxybenzyl-sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using (4-methoxyphenyl) methanethiol, the title compound was obtained as a brown solid by the same process as in Example 452, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.32 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.61 and 3.79 (total 3H, each s), 4.05 and 4.40 (total 2H, each s), 6.69 and 6.79 (total 2H, each d, J = 8.6 Hz), 6.88-7.52

(5H, m), 7.98 and 8.01 (total 1H, each d, J = 8.6 Hz), 8.44 and 8.46 (total 1H, each d, J = 2-9 Hz), 8.58-8.65 (1H, m), 8.68 and 8.70 (total 1H, each d, J = 2.5 Hz), 9.58 and 9.74 (d, J = 114 Hz), 10.05 and 10.46 (total 1H, each brs).

ESI-MS (m/e): 534 (M+H).

Example 455

4-(6-cyano-pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy) -2-pyrazin-2-yl -1H-benzimidazole

Using 2-chloro-3-cyanopyridine, the title compound was obtained as a pale yellow solid by the same process as in Example 446, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.32 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.20 (1H, dd, J = 7.8, 4.9 Hz), 7.41 (1H, d, J = 2.2 Hz), 7.45 (1H, dd, J = 8.8, 2.8 Hz), 7.72 (1H, d, J = 2.2 Hz), 7.93 (1H, dd, J = 7.8, 1.8 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.44 (1H, dd, J = 4.9, 2.0 Hz), 8.54 (1H, d, J = 2.8 Hz), 8.62 (1H, dd, J = 2.5, 1, 5 Hz), 8.70 (1H, d, J = 2.5 Hz), 9.64 (1H, d, J = 1.5 Hz).

ESI-MS (m/e): 516 (M+H).

Example 456

4-(2-cyano-pyridin-3-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2-cyano-3-fluoropyridine and 4-mercapto-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 455, the title compound was obtained as pale yellow solid by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 1.13 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.22 (1H, s), 7.41 (1H, s), 7.64 (2H, dd, J = 8.6, 2.7 Hz), 7.96-8.04 (2H, m), 8.59-8.66 (2H, m), 8.77-8.83 (2H, m), 9.32 (1H, s).

ESI-MS (m/e): 516 (M+H).

Example 457

4-(pyridin-2-yl sulphanyl)-5-chloro-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl -1H-benzimidazole

Using pyridine-2-thiol, the title compound was obtained as a pale yellow solid by the same procedures as in Example 117 and Example 290, a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.31 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.2 (1H, d, J = 7.5 Hz), 7.05-7.10 (1H, m), 7.31 (1H, dd, J = 8.6, 2.7 Hz), 7.41 (1H, t, J = 6.0 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.75 (1H, s), 7.88 (1H, t, J = 7.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.41 (1H,

d, J = 4.1 Hz), 8.50 (1H, d, J = 2.5 Hz), 8.63 (1H, s).

ESI-MS (m/e): 524,526 (M+H).

Examples 458-1, 458-2

4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

and

4-(pyridin-2-yl sulfonyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

To methanol 3 ml solution of 4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole 20 mg obtained in Example 451 were added OXONE 50 mg and water 0.5 ml, and the reaction liquor was stirred at room temperature for three hours. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was diluted with ethyl acetate and was washed with water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. Saturated aqueous sodium bicarbonate was added to the obtained fraction and thereafter, it was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 1.33 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.35 (1H, dd, J = 8.8, 2.7 Hz), 7.37-7.45 (2H, m), 7.55 (1H, d, J = 2.1 Hz), 7.61 (1H, d, J = 2.1 Hz), 7.89 (1H, t, J = 7.8 Hz), 7.96 (1H, t, J = 7.8 Hz), 8.02 (1H, d, J = 8.6 Hz), 8.15 (1H, d, J = 8.2 Hz), 8.37 (1H, d, J = 7.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.65 (1H, d, J = 3.7 Hz), 8.76 (1H, d, J = 4.5 Hz).

ESI-MS(m/e): 506 (M+H).

4-(pyridin-2-yl sulfonyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

¹H-NMR (CDCl₃) δ : 1.33 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.37 (1H, dd, J = 8.6, 2.8 Hz), 7.44-7.49 (1H, m), 7.55 (1H, dd, J = 7.4, 4.5 Hz), 7.70 (1H, d, J = 1, 8 Hz), 7.80 (1H, d, J = 2.2 Hz), 7.88-7.94 (1H, m), 7.96-8.02 (1H, m), 8.04 (1H, d, J = 8.6 Hz), 8.26 (1H, d, J = 7.4 Hz), 8.40 (1H, d, J = 8.0 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.73 (1H, d, J = 4.7 Hz), 8.77 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 522 (M+H).

Example 4596-(1-acetyl pyrrolidin-2-yl)-5-((2'-fluoro biphenyl-4-yl) oxy)-2-pyridin-2-yl-1H- benzimidazole

Using 2'-fluoro biphenyl-4-ol, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.00-2.60 (7H, m), 3.40-4.00 (2H, m), 5.20-5.65 (1H, m), 7.00-7.70 (11H, m), 7.80-8.00 (1H, m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, 1).

ESI-MS (m/e): 493 (M+H).

Example 4606-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H- benzimidazole • monotrifluoroacetic acid salt**Step 1**Synthesis of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde

To N-methyl-2-pyridone 1 ml solution of 1-(2-(6-hydroxy-2-pyridin-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 100 mg obtained in Example 121 (Step 11) were added successively cesium carbonate 143 mg, p-fluoro benzaldehyde 0.048 ml, and the reaction liquor was heated with stirring at 80°C for three hours. The reaction liquor was cooled to room temperature, and saturated ammonium chloride aqueous solution was added, and the mixture was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution. After drying, the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 100/1) and the title compound was obtained as orange oily substance.

Step 2Synthesis of 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H -benzimidazole

To chloroform 0.2 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde 22 mg, bis (2-methoxyethyl) amino sulphur trifluoride 0.036 ml was added, and the reaction liquor was heated with stirring at 80°C for eight hours. The solvent was eliminated by distillation under reduced pressure, then the residue was purified by preparative thin layer chromatography (Kieselgel TM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1), and the title compound was obtained as yellow solid.

Step 3

Production of 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • monotrifluoroacetic acid salt

Trifluoroacetic acid 0.5 ml was added to 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole 12 mg, and the reaction liquor was stirred at room temperature for one hour. Trifluoroacetic acid was eliminated by distillation under reduced pressure, and thereafter the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as red oily substance.

¹H-NMR(CD₃OD) δ : 0.78-0.95 (4H, m), 1.91-2.15 (2H, m), 2.69 (3H, s), 5.38-5.43 (1H, m), 7.21-7.34 (4H, m), 7.52-7.63 (6H, m), 8.27-8.29 (1H, m).

ESI-MS (m/e): 449 (M+H).

Example 461

1-(2-(6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (3-chloro-4-methanesulphonyl) phenol, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.85-2.40 (4H, m), 2.90-3.27 (5H, m), 3.65-3.90 (2H, m), 5.15-5.43 (1H, m), 6.90-7.45 (5H, m), 7.84-8.15 (2H, m), 8.35-8.42 (1H, m), 8.60-8.68 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 462

2-(6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methanesulphonyl) phenoxy)-1H-benzimidazol-2-yl) (1,3) thiazolo (5,4-b) pyridine • monotrifluoroacetic acid salt

Using 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained in Example 306 (Step 3) and (1,3) thiazolo (5,4-b) pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 306 (Step 4) and (Step 5), by a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.60-2.40 (7H, m), 3.00-3.80 (5H, m), 5.00-5.60 (1H, m), 7.20-7.40 (2H, m), 7.25-7.80 (3H, m), 7.90-8.10 (2H, m), 8.40-8.80 (2H, m).

ESI-MS (m/e): 534 (M+H).

Example 463

5-(1-acetyl pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-(5-(trifluoromethyl)

pyridin-2-yl)-1H-benzimidazole

Using 5-(trifluoromethyl) pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 462, by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 0.89 (1H, m), 1.22 (2H, m), 1.88-2.11 (3H, m), 2.27 (1H, m), 3.08 (3H, m), 3.63-3.76 (1H, m), 3.84 (1H, s), 5.38 (1H, dd, J = 25.8, 8.6 Hz), 7.11-7.20 (2H, m), 7.39 (1H, m), 7.54 (1H, m), 7.93 (2H, m), 8.11 (1H, m), 8.51 (1H, m), 8.93 (1H, m), 10.58-10.88 (1H, m).

ESI-MS (m/e): 545 (M+H).

Example 4646-(1-acetyl pyrrolidin-2-yl)-2-(5-(difluoromethyl) pyridin-2-yl)-5-(4-methanesulphonyl phenoxy)-1H-benzimidazole • monotrifluoroacetic acid salt

Using 5-(difluoromethyl) pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 0.92 (1H, m), 1.32 (2H, m), 1.89 (1H, m), 1.97-2.08 (2H, m), 2.13-2.14 (1H, m), 2.69 (3H, s), 3.16-3.17 (3H, s), 5.35 (1H, m), 7.30-7.32 (1H, m), 7.41-7.58 (1H, m), 7.60-7.62 (1H, m), 8.00-8.02 (3H, m), 8.04-8.22 (2H, m), 9.04 (1H, m).

ESI-MS (m/e): 527 (M+H).

Example 4656-(1-acetyl pyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl- 1H-benzimidazole • monotrifluoroacetic acid salt

To methanol 0.5 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol -5-yl) oxy) benzaldehyde 50 mg obtained in Example 460 (Step 1) was added hydroxylation boron sodium 7 mg under ice cooling, and the reaction liquor was stirred for one hour. Saturated ammonium chloride aqueous solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To dimethylformamide 1 ml solution of the obtained crude product, sodium hydride 10 mg and methyl iodide 0.030 ml were added successively and stirred at room temperature for 30 minutes. Saturated ammonium chloride aqueous solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Trifluoroacetic acid 0.5 ml was added to the obtained crude product, and the reaction liquor was

stirred at room temperature for two hours. Trifluoroacetic acid was eliminated by distillation under reduced pressure, and thereafter the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

¹H-NMR(CD₃OD) δ : 1.93 (1H, m), 2.07-2.11 (3H, m), 2.18 (2H, m), 2.45 (1H, m), 3.43 (3H, d, J = 3-Hz), 3.75-3.95 (2H, m), 4.50 (d, 2H, J = 4-3 Hz), 5.49-5.56 (1H, m), 7.16 (3H, m), 7.44-7.49 (2H, m), 7.57 (1H, m), 7.70-7.73 (1H, m), 8.15 (1H, m), 8.27-8.30 (1H, m), 8.89 (1H, m).

ESI-MS (m/e): 443 (M+H).

Example 466

1-(4-(6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanol • monotrifluoroacetic acid salt

To tetrahydrofuran 1.3 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde 70 mg obtained in Example 460 (Step 1) was added methyllithium (1.0M diethyl ether solution) 0.4 ml at -78°C, and the reaction liquor was stirred at 78°C for 30 minutes. Saturated ammonium chloride solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Trifluoroacetic acid 0.5 ml was added to the obtained crude product and stirred at room temperature for 90 minutes, and thereafter, trifluoroacetic acid was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

¹H-NMR(CD₃OD) δ : 0.90-0.96 (1H, m), 1.31 (4H, m), 1.25-1.90 (3H, m), 2.42 (1H, m), 2.68 (3H, s), 3.89-3.91 (1H, m), 5.50 (1H, m), 7.02-7.33 (4H, m), 7.42-7.52 (2H, m), 7.59-7.67 (1H, m), 8.10-8.14 (1H, m), 8.22-8.26 (1H, m), 8.80-8.87 (1H, m).

ESI-MS (m/e): 443 (M+H).

Example 467

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(3-methyl-[1,2,4]-oxadiazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 5-(4-iodophenyl)-3-methyl-[1,2,4]-oxadiazole, the title compound was obtained as dark brown oily substance by the same process as in Example 122, a process based on this or a

combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.39-2.49 (10H, m), 3.42-3.88 (2H, m), 5.14-5.4 (1H, m), 6.70-8.69 (10H, m).

ESI-MS (m/e): 481 (M+H).

Example 468

(1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A

Step 1

Synthesis of 3-((t-butyl (dimethyl) silyl) oxy) dihydrofuran-2 (3H)-one

In 3-hydroxy dihydrofuran-2 (3H)-one 9.0 g dissolved in dimethylformamide 180 ml were added successively imidazole 9.0 g, t-butyl dimethylsilyl chloride 15.9 g, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with ethyl acetate and was washed using water, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as colourless oily supplies.

Step 2

Synthesis of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-4-hydroxy butanoyl)-3-fluorophenyl) pyridine-2-carboxamide

In N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.1 g dissolved in tetrahydrofuran 100 ml, n-butyllithium (2.66M hexane solution) 3.1 ml was added dropwise at -78°C, and the reaction liquor was stirred at the same temperature for 15 minutes. 3-((t-butyl (dimethyl) silyl) oxy) dihydrofuran-2 (3H)-one 1.21 g was added to the reaction liquor, and the reaction liquor was stirred at the same temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and it was warmed to room temperature, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1), and the title compound was obtained as a colourless oily substance.

Step 3

Synthesis of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-1,4-dihydroxy butyl)-3-fluorophenyl) pyridine-2-carboxamide

To methanol 20 ml solution of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-4-hydroxy butanoyl)-3-fluorophenyl) pyridine-2-carboxamide 860 mg was added sodium borohydride 114

mg under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1) and the title compound was obtained as a white solid.

Step 4

Synthesis of N-(4-(3-((t-butyl (dimethyl) silyl) oxy) pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide

Triethylamine 155 mg and methanesulfonyl chloride 130 mg were added under ice cooling successively to chloroform 8 ml solution of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-1,4-dihydroxybutyl)-3-fluorophenyl) pyridine-2-carboxamide 165 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 5 ml solution of the obtained residue was added sodium azide 25 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and sodium borohydride 50 mg and copper sulfate • pentahydrate 5 mg were added successively to methanol 10 ml solution of the obtained residue, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, saturated aqueous sodium bicarbonate was added and was extracted with chloroform, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 50/1) and the title compound was obtained as a colourless oily substance.

Step 5

Synthesis of 1-acetyl-2-(2-fluoro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate

To methanol 1 ml solution of N-(4-(3-((t-butyl (dimethyl) silyl) oxy) pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide 59 mg was added 4 N hydrochloric acid-dioxane 2 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and triethylamine 100 mg, acetic anhydride 90 mg, N,N-4-dimethylaminopyridine 5 mg were added successively to chloroform 5 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure and the obtained

residue was purified using silica gel chromatography (eluent: chloroform / methanol = 200/1), and obtained the title compound as a colourless oily substance.

Step 6

Synthesis of 1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate diastereomer A and diastereomer B

Fuming nitric acid 1 ml was added to N-(4-(3-((t-butyl (dimethyl) silyl) oxy)-pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide 57 mg, and the reaction liquor was stirred at room temperature for 40 minutes. The reaction liquor was discharged into mixed solution of ice-saturated aqueous sodium bicarbonate and was extracted with chloroform, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Corporation), chloroform/methanol = 20/1), and respectively obtained diastereomer A and diastereomer B of the title compound as a yellow oily substance.

Step 7

Production of 1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A

Using 4-(methanesulphonyl) phenol and (1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate diastereomer A, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.86-2.42 (8H, m), 3.04-3.10 (3H, m), 3.72-4.02 (2H, m), 5.06-5.38 (2H, m), 7.08-7.70 (5H, m), 7.83-7.97 (3H, m), 8.34-8.42 (1H, m), 8.61-8.68 (1H, m), 10.54-10.65-(1H, m).

ESI-MS (m/e): 535 (M+H).

Example 469

1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-ol diastereomer A

To methanol 2 ml solution of (1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A 14 mg obtained in Example 468 was added potassium carbonate 5 mg, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Corporation), chloroform/methanol = 15/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 1.82-2.47 (5H, m), 3.05&3.08 (3H, s), 3.70-3.97 (2H, m), 4.29-4.45 (1H, m), 5.00-5.32 (1H, m), 7.00-7.67 (5H, m), 7.81-7.96 (2H, m), 8.00-8.42 (1H, m), 8.60-8.69 (1H, m), 10.62-10.85 (1H, m).

ESI-MS (m/e): 493 (M+H).

Example 470

6-(1-acetyl-4,5-dihydro-1H-pyrrole-2-yl)-5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To chloroform 1 ml solution of 1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-ol diastereomer A 2 mg obtained in Example 469 was added bis (2-methoxyethyl) amino sulphur trifluoride 2 mg, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Corporation), chloroform/methanol = 15/1), and obtained the title compound as a colourless oily substance.

¹H-NMR (CDCl₃) δ : 1.40-4.43 (10H, m), 7.03-7.80 (6H, m), 7.82-7.95 (3H, m), 8.32-8.46 (1H, m), 8.60-8.71 (1H, m), 10.38-10.60 (1H, m).

ESI-MS (m/e): 475 (M+H).

Example 471

1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)pyrrolidin-3-yl acetate diastereomer B

Using (1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl) diastereomer B obtained in Example 468 (Step 6), the title compound was obtained by the same process as in Example 468 (Step 7), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.72-2.30 (8H, m), 3.02-3.08 (3H, m), 3.64-3.99 (2H, m), 5.26-5.47 (1H, m), 5.58-5.72 (1H, m), 7.09-7.73 (5H, m), 7.82-7.94 (3H, m), 8.33-8.43 (1H, m), 8.60-8.70 (1H, m), 10.47-10.68 (1H, m).

ESI-MS (m/e): 535 (M+H).

Example 472

1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)pyrrolidin-3-ol diastereomer B

Using (1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)pyrrolidin-3-yl acetate diastereomer B obtained in Example 471, the title compound was obtained by the same process as in Example 469, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.78-2.25 (5H, m), 3.03-3.10 (3H, m), 3.60-4.00 (2H, m), 4.50-4.68 (1H, m), 5.27-5.45 (1H, m), 7.03-7.73 (5H, m), 7.81-7.96 (3H, m), 8.32-8.45 (1H, m), 8.60-8.69 (1H, m), 10.51-10.82 (1H, m).

ESI-MS (m/e): 493 (M+H).

Example 473

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) piperidin-2-one

Using 1-(4-hydroxyphenyl) piperidin-2-one, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.74-2.62 (13H, m), 3.52-3.87 (4H, m), 5.18-5.36 (1H, m), 6.71-7.64 (7H, m), 7.76-7.90 (1H, m), 8.26-8.41 (1H, m), 8.56-8.68 (1H, m), 10.98-11.33 (1H, m).

ESI-MS (m/e): 496 (M+H).

Example 474

6-(1-acetyl pyrrolidin-2-yl)-5-((6-phenyl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-phenyl pyridin-3-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.40-2.50 (7H, m), 3.40-4.00 (2H, m), 5.20-5.60 (1H, m), 6.90-8.00 (11H, m), 8.20-8.45 (1H, m), 8.50-8.70 (2H, m), 10.60-10.90 (1H, m).

ESI-MS (m/e): 476 (M+H).

Example 475

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-fluorophenyl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(2-fluorophenyl) pyridin-3-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.50 (7H, m), 3.45-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.05 (10H, m), 8.30-8.45 (1H, m), 8.50-8.70 (2H, m), 10.80-11.20 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 476

1-(2-(6-(3-fluoro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (3-fluoro-4-methanesulphonyl) phenol, the title compound was obtained as yellow solid by

the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.87-2.38 (4H, m), 2.85-3.27 (5H, m), 3.60-3.95 (2H, m), 5.20-5.41 (1H, m), 6.83-7.00 (1H, m), 7.28-7.40 (4H, m), 7.81-7.98 (2H, m), 8.35-8.42 (1H, m), 8.60-8.68 (1H, m).

ESI-MS (m/e): 495 (M+H).

Example 477

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyrrolidin-2-one

Using 1-(4-hydroxyphenyl) pyrrolidin-2-one, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.40 (6H, m), 2.62 (2H, m), 3.55-3.95 (4H+1/2H, m), 5.28 (1/2H, m), 6.90-7.10 (3H, m), 7.35 (1H+1/2H, m), 7.45-7.65 (2H+1/2H, m), 7.85 (1H, m), 8.34 (1H, m), 8.61 (1H, m), 10.4-10.8 (1H, br).

ESI-MS (m/e): 482 (M+H).

Example 478

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridine-2 (1H)-one

Using 1-(4-hydroxyphenyl) pyridine-2 (1H)-one, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.72-2.42 (7H, m), 3.48-3.86 (2H, m), 5.15-5.52 (1H, m), 6.19-6.32 (1H, m), 6.61-6.73 (1H, m), 6.80-7.66 (9H, m), 7.77-7.89 (1H, m), 8.32-8.41 (1H, m), 8.52-8.65 (1H, m), 11.07-11.48 (1H, m).

ESI-MS (m/e): 492 (M+H).

Example 479

5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yl) oxy)-2,2'-bipyridine • monotrifluoroacetic acid salt

Using 2,2'-bipyridine-5-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.80-2.80 (7H, m), 3.160-4.05 (2H, m), 5.20-5.60 (1H, m), 7.50-7.90 (4H, m), 8.00-8.15 (1H, m), 8.15-8.25 (1H, m), 8.30-8.40 (1H, m), 8.45-8.60 (1H, m), 8.60-9.00 (5H, m).

ESI-MS (m/e): 477 (M+H).

Example 480

N-(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-methane sulfonamide

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) and N-t-butoxycarbonyl-glycine, the title compound was obtained by the same procedures as in Example 171 and Example 178, a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.93-2.14 (3H, m), 2.06-2.27 (1H, m), 2.86 and 2.95 (total 3H, each s), 3.13 (3H, s), 3.43-4.08 (4H, m), 5.20-5.38 (1H, m), 7.20-7.60 (5H, m), 7.93-8.02 (3H, m), 8.23-8.30 (1H, m), 8.74 (1H, brs).

ESI-MS (m/e): 570 (M+H).

Example 481

(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-ethyl carbamate ester

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) and N-t-butoxycarbonyl-glycine, the title compound was obtained by the same procedures as in Example 171 and Example 181, a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.18 and 1.23 (total 3H, each t, J = each 7.1 Hz), 1.93-2.14 (3H, m), 2.22-2.44 (1H, m), 3.12 and 3.13 (total 3H, each s), 3.30-4.13 (6H, m), 5.24-5.33 (1H, m), 7.20-7.60 (5H, m), 7.93-8.01 (3H, m), 8.28 (1H, t, J = 8.2 Hz), 8.73 (1H, brs).

ESI-MS (m/e): 564 (M+H).

Example 482

6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer

A

Step 1

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2- carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide 100 mg obtained by Example 338 (Step 4) was optically-resolved by a column for optical resolution (CHIRALPAK OD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 60/40/0.1, flow rate: 10 ml/min), and enantiomer A (retention time: 17.8 min), enantiomer B (retention time: 21.0 min) were respectively obtained as pale yellow solid.

Step 2

Production of 6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Using N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer A obtained in Example 482 (Step 1) and 4-bromo(sic)phenol, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

¹H-NMR, (CDCl₃) δ : 1.56-2.41 (7H, m), 3.42-3.90 (2H, m), 5.16-5.51 (1H, m), 6.78-7.66 (7H, m), 7.80-7.93 (1H, m), 8.32-8.44 (1H, m), 8.54-8.67 (1H, m), 11.14-11.65 (1H, m).

ESI-MS (m/e): 479 (M+H).

Example 483

6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

Using N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 482 (Step 1) and 4-bromo(sic)phenol, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

ESI-MS (m/e): 479 (M+H).

Examples 484

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.51-2.43 (7H, m), 2.59-2.74 (3H, m), 3.50-3.93 (2H, m), 5.17-5.46 (1H, m), 7.00-7.72 (4H, m), 7.82-8.13 (2H, m), 8.34-8.44 (1H, m), 8.57-8.69 (2H, m), 10.75-11.14 (1H, m).

ESI-MS (m/e): 482 (M+H).

Example 485

5-(1-acetyl-3-methylpyrrolidin-2-yl)-6-(4-(methylsulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Step 1

Synthesis of N-(3-fluoro-4-[2-(2-hydroxyethyl) acryloyl] phenyl) pyridine-2-carboxamide

To N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.0 g dissolved in tetrahydrofuran 20 ml solution, 60 % sodium hydride 136 mg was added under ice cooling, and the reaction liquor was

stirred at the same temperature for 15 minutes. The reaction liquor was cooled to -78°C , and thereafter, n-butyllithium (2.66M hexane solution) 1.53 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 30 minutes. 3-methylene dihydro-furan-2(3H)-one 0.36 ml was added to the reaction liquor at the same temperature, and the reaction liquor was stirred at the same temperature for two hours, and thereafter, it was warmed to 0°C , and it was stirred for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and the mixture was extracted with ethyl acetate, and the organic layer was washed using saturated aqueous sodium chloride solution, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained as a colourless oily substance.

Step 2

Synthesis of N-(4-[1,4-dihydroxy-2-methyl butyl]-3-fluorophenyl) pyridine-2-carboxamide

To methanol 8 ml solution of N-(3-fluoro-4-(2-[2-hydroxyethyl) acryloyl) phenyl) pyridine-2-carboxamide 320 mg, sodium borohydride 150 mg was added, and the reaction liquor was stirred at room temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform / methanol = 100/1) and the title compound was obtained as a colourless oily substance.

Step 3

Synthesis of N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide

To chloroform 5 ml solution of N-(4-(1,4-dihydroxy-2-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide 100 mg were added successively triethylamine 0.18 ml, methanesulfonyl chloride 0.07 ml, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 4 ml solution of the obtained residue was added sodium azide 23 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled to room temperature, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and, to methanol 5 ml solution of the obtained residue were added successively sodium borohydride 50 mg, copper sulfate • pentahydrate 5 mg, and the reaction liquor was stirred at 40°C for 15 minutes. The reaction liquor was cooled to room temperature, and thereafter, saturated aqueous sodium bicarbonate was added, extraction was carried out with chloroform and dried with anhydrous

sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 4 ml solution of the obtained residue were added successively triethylamine 0.08 ml, acetic anhydride 0.07 ml, N,N-4-dimethylaminopyridine 5 mg, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform / methanol = 100/1) and the title compound was obtained as a colourless oily substance.

Step 4

Synthesis of N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide

Fuming nitric acid 1 ml was added to N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide 70 mg, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was discharged into ice-saturated aqueous sodium bicarbonate mixed solution, extracted with chloroform, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and thereby obtained the title compound as yellow solid.

Step 5

Production of 5-(1-acetyl-3-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide and 4-(methanesulphonyl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 0.81-2.73 (9H, m), 3.03-3.11 (3H, m), 3.36-3.99 (2H, m), 4.65-5.43 (1H, m), 7.00-7.75 (5H, m), 7.81-7.79 (3H, m), 8.32-8.45 (1H, m), 8.60-8.68 (1H, m), 10.51-10.82 (1H, br).

ESI-MS (m/e): 491 (M+H).

Example 486

6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1(2H)-one

Using 6-hydroxy-3,4-dihydro-naphthalene-1(2H)-one, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.00-3.00 (13H, m), 3.40-3.95 (2H, m), 5.00-5.50 (1H, m), 6.60-7.80 (5H, m), 7.80-8.20 (2H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m), 10.80-11.20 (1H, m).

ESI-MS (m/e): 467 (M+H).

Example 487

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1H-imidazol-1-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1H-imidazol-1-yl) phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.00-2.50 (7H, m), 3.50-4.50 (2H, m), 5.20-6.00 (1H, m), 6.80-8.80 (13H, 13).

ESI-MS (m/e): 465 (M+H).

Example 488

6-(((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-1-methyl-[1,2,3,4]-tetrahydronaphthalene-1-ol

To tetrahydrofuran 0.5 ml solution of 6-(((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1 (2H)-one 7 mg obtained in Example 486 was added methylmagnesium bromide (5.0M tetrahydrofuran solution) 0.050 ml under ice cooling, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with chloroform, washed with saturated ammonium chloride aqueous solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound was obtained as a colourless oily substance.

¹H-NMR (CDCl₃) δ : 1.10-2.80 (16H, m), 3.50-4.00 (2H, m), 5.10-5.50 (1H, m), 6.60-7.90 (7H, m), 8.30-8.50 (1H, m), 8.50-70 (1H, m).

ESI-MS (m/e): 465 (M+H).

Example 489

6-(((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-[1,2,3,4]-tetrahydronaphthalene-1-ol

To tetrahydrofuran 0.5 ml solution of 6-(((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1 (2H)-one 7 mg obtained in Example 486 was added sodium borohydride 5 mg under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform, washed with saturated ammonium chloride aqueous solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced

pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a colourless oily substance.

¹H-NMR (CDCl₃) δ : 1.00-2.50 (14H, m), 4.00-6.00 (3H, m), 6.80-8.50 (9H, m).

ESI-MS (m/e): 469 (M+H).

Example 490

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer A

Step 1

Synthesis of ethyl (2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoate

Tetrahydrofuran 40 ml solution of (diethoxy phosphoryl) (fluoro) ethyl acetate 2.0 g was cooled to -78°C, and thereafter, n-butyllithium (2.66M hexane solution) 3.4 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 15 minutes. To the reaction liquor was added ((t-butyl (dimethyl) silyl) oxy) acetaldehyde 2.1 ml, and the reaction liquor was stirred at the same temperature for two hours. Saturated aqueous sodium bicarbonate was added to the reaction solution at the same temperature, and it was warmed to room temperature, and thereafter, extraction was carried out with ethyl acetate. It was dried using anhydrous sodium sulfate, and next the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 50/1) and the title compound was obtained as a colourless oily substance.

Step 2

Synthesis of N-(4-((2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoyl)-3-fluorophenyl)pyridine-2-carboxamide

To N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.0 g dissolved in tetrahydrofuran 40 ml solution, 60 % sodium hydride 136 mg was added under ice cooling, and the reaction liquor was stirred at the same temperature for 20 minutes. The reaction liquor was cooled to -78°C, and thereafter, n-butyllithium (2.66M hexane solution) 1.53 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 20 minutes. Ethyl (2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoate 1.07 g was added to the reaction liquor at the same temperature, and the reaction liquor was stirred at the same temperature for four hours. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and it was warmed to room temperature, and thereafter, it was extracted with ethyl acetate, and the organic layer was washed using saturated aqueous sodium chloride solution, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 3/1) and the title

compound was obtained as a colourless oily substance.

Step 3

N-(4-(4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro-1-hydroxy butyl)-3-fluorophenyl) pyridine-2-carboxamide

To methanol 20 ml solution of N-(4-((2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro but-2-enoyl)-3-fluorophenyl) pyridine-2-carboxamide 300 mg was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for four hours. The catalyst was filtered, and the solvent was eliminated by distillation under reduced pressure, and, to methanol 4 ml solution of the obtained residue was added sodium borohydride 50 mg, and the reaction liquor was stirred at room temperature for one hour.

Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1) and the title compound was obtained as a colourless oily substance.

Step 4

Synthesis of N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereoisomer A and diastereomer B

To chloroform 5 ml solution of N-(4-(4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro-1-hydroxybutyl)-3-fluorophenyl) pyridine-2-carboxamide 100 mg were added successively triethylamine 46 mg, methanesulfonyl chloride 39 mg, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 4 ml solution of the obtained residue was added sodium azide 22 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and tetrabutyl ammonium fluoride (1.0M tetrahydrofuran solution) 0.3 ml was added to tetrahydrofuran 4 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for one hour. To the reaction liquor, water was added and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 5 ml solution of the obtained residue were added successively triethylamine 46 mg, methanesulfonyl chloride 39 mg,

and the reaction liquor was stirred at room temperature for 30 minutes. To the reaction liquor, saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and copper sulfate • pentahydrate 10 mg, sodium borohydride 50 mg were added successively to methanol 4 ml solution of the obtained residue, and the reaction liquor was stirred at 40°C for one hour. The reaction liquor was cooled, and thereafter, saturated aqueous sodium bicarbonate was added, and extraction was carried out with chloroform and the chloroform layer was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 4 ml solution of the obtained residue were added successively triethylamine 46 mg, acetic anhydride 35 mg, N,N-4-dimethylaminopyridine 5 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using preparative thin layer chromatography (chloroform/methanol = 30/1) and the title compounds diastereomer A and diastereomer B were respectively obtained as a colourless oily substance.

Step 5

Production of 5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer A

Fuming nitric acid 0.5 ml was added to N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereomer A 18 mg, and the reaction liquor was stirred at room temperature for ten minutes. The reaction liquor was discharged into ice-saturated aqueous sodium bicarbonate mixed solution, extracted with chloroform, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Using the obtained composition(sic) product and 4-(methanesulphonyl) phenol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.85-2.40 (5H, m), 3.06 and 3.09 (3H, s), 3.79-4.08 (2H, m), 4.96-5.62 (2H, m), 7.05-7.70 (5H, m), 7.83-7.99 (3H, m), 8.34-8.43 (1H, m), 8.61-8.69 (1H, m), 10.58-10.84 (1H, m).

ESI-MS (m/e): 495 (M+H).

Example 491

6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-(4-(2-thienyl) phenoxy)-1H-benzimidazole

Using 4-(2-thienyl) phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.05-2.45 (7H, m), 3.40-4.00 (2H, m), 5.10-5.60 (1H, m), 6.80-8.00 (11H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 481 (M+H).

Example 492

2-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1H-iso indole-1,3 (2H)-dione

Using 2-(4-hydroxyphenyl)-1H-iso indole-1,3 (2H) dione, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.05-2.40 (7H, m), 3.40-4.05 (2H, m), 5.05-5.60 (1H, m), 6.80-8.20 (12H, m), 8.30-8.70 (2H, m).

ESI-MS (m/e): 544 (M+H).

Example 493

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer B

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereomer B obtained by Example 490 (Step 4), the title compound was obtained as pale yellow solid in accordance with Example 490 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.45 (5H, m), 3.05 and 3.08 (3H, s), 3.61-4.31 (2H, m), 5.08-5.54 (2H, m), 7.03-7.80 (5H, m), 7.81-7.97 (3H, m), 8.33-8.43 (1H, m), 8.60-8.68 (1H, m), 10.52-10.75 (1H, 1).

ESI-MS (m/e): 495 (M+H).

Example 494

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-1H-tetrazol-1-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(5-methyl-1H-tetrazol-1-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ: 1.91 and 2.15 (total 3H, each s), 1.97-2.20 (3H, m), 2.22-2.58 (1H, m), 2.63 and 2.64 (total 3H, each s), 3.62-4.00 (2H, m), 5.34-5.42 (1H, m), 7.22-7.68 (7H, m), 7.94-8.05 (1H, m), 8.30 (1H, t, J = 7.8 Hz), 8.76 (1H, brs).

ESI-MS (m/e): 481 (M+H).

Example 495

Ethyl 5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)
pyridine-2-carboxylate

Using ethyl 5-hydroxypyridine-2-carboxylate, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.30-1.50 (3H, m), 1.50-2.50 (7H, m), 3.50-3.90 (2H, m), 4.35-4.60 (2H, m), 5.10-5.45 (1H, m), .6.90-7.70 (4H, m), 7.80-7.95 (1H, m), 8.00-8.20 (1H, m), 8.30-8.80 (3H, m), 10.60-11.20 (1H, m).

ESI-MS (m/e): 472 (M+H).

Example 496

6-(1-acetyl pyrrolidin-2-yl)-5-(4-pyrazin-2-yl phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-pyrazin-2-yl phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 0.80-2.40 (7H, m), 3.60-3.90 (2H, m), 5.20-5.60 (1H, m), 6.80-8.05 (8H, m), 8.30-8.80 (4H, m), 8.90-9.10 (1H, m), 10.40-10.80 (1H, m).

ESI-MS (m/e): 477 (M+H).

Example 497

6-(1-acetyl pyrrolidin-2-yl)-5-(1H-indol-5-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 1H-indole-5-ol, title-compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.20-2.40 (7H, m), 3.60-4.00 (2H, m), 5.20-5.60 (1H, m), 6.40-6.60 (1H, m), 6.80-8.00 (7H, m), 8.20-8.50 (2H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 438 (M+H).

Example 498

(2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)
pyrrolidin-1-yl)-2-oxoethyl) methylamine

Step 1

Synthesis of (3-fluoro-4-pyrrolidin-2-yl phenyl) amine dihydrochloride

To mixed solution of methanol 50 ml and ethyl acetate 50 ml of

2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 19 g obtained in Example 338 (Step 2) was added 4 N hydrochloric acid-dioxane solution 100 ml under ice cooling, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid.

Step 2Synthesis of 2,2,2-trifluoro-N-(3-fluoro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide

To (3-fluoro-4-pyrrolidin-2-yl phenyl) amine dihydrochloride 20 g suspended in chloroform 200 ml were added successively pyridine 39 ml and trifluoroacetic anhydride 24 ml under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as brown oily substance.

Step 3Synthesis of 2,2,2-trifluoro-N-(5-fluoro-2-nitro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide

Fuming nitric acid 100 ml was added under ice cooling to 2,2,2-trifluoro-N-(3-fluoro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide 28 g, and the reaction liquor was stirred at room temperature for one hour. Iced water was added to the reaction liquor and, after dilution, it was extracted with ethyl acetate and washed using saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 10/1) and the title compound was obtained as a yellow oily substance.

Step 4Synthesis of t-butyl 2-(4-amino-2-fluoro-5-nitrophenyl) pyrrolidine-1-carboxylate

To 2,2,2-trifluoro-N-(5-fluoro-2-nitro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide 29 g dissolved in tetrahydrofuran 150 ml, were added 1N sodium hydroxide aqueous solution 150 ml under ice cooling, and the reaction liquor was stirred at room temperature for five hours. Furthermore, di t-butyl dicarbonate 23 ml was added to the reaction liquor and the reaction liquor was stirred for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as a yellow solid

Step 5Synthesis of t-butyl 2-(4-amino-2-((2'-fluorobiphenyl-4-yl) oxy)-5-nitrophenyl) pyrrolidine-1-carboxylate

To N,N-dimethylformamide 3 ml solution of t-butyl 2-(4-amino-2-fluoro-5-nitrophenyl) pyrrolidine-1-carboxylate 288 mg were added 2'-fluorobiphenyl-4-ol 200 mg and potassium carbonate 184 mg, and the reaction liquor was stirred overnight at 80°C. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as a yellow solid

Step 6

Synthesis of t-butyl 2-(4,5-diamino-2-((2'-fluorobiphenyl-4-yl) oxy) phenyl) pyrrolidine-1-carboxylate

To methanol 5 ml solution of t-butyl 2-(4-amino-2-((2'-fluorobiphenyl-4-yl) oxy)-5-nitrophenyl) pyrrolidine-1-carboxylate 410 mg was added development Raney nickel catalyst 1 ml, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for a whole day. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained as brown oily substance.

Step 7

Synthesis of 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole

To methanol 5 ml solution of t-butyl 2-(4,5-diamino-2-((2'-fluorobiphenyl-4-yl) oxy) phenyl) pyrrolidine-1-carboxylate 255 mg were added N-((1E)-pyridin-2-ylmethylene) aniline (1M methanol solution) 1.6 ml, and the reaction liquor was stirred at 90°C for a whole day. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and 4 N hydrochloric acid-dioxane solution 5 ml was added to the obtained residue 332 mg, and the reaction liquor was stirred at room temperature for three hours. The solvent was eliminated by distillation under reduced pressure, and extraction was carried out with chloroform after dilution with saturated aqueous sodium bicarbonate. The organic layer was washed using saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was refined by silica gel column chromatography (eluent: chloroform-methanol / ammonia water solution = 20/1/0.1) and the title compound was obtained as a yellow oily substance.

Step 8**Production of (2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl)-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine**

To pyridine 1 ml solution of 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole 37 mg were added successively N-(t-butoxy carbonyl)-N-methylglycine 19 mg, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 24 mg, and the reaction liquor was stirred at room temperature for three hours. 4 N hydrochloric acid-dioxane solution 2 ml was added to the reaction liquor, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with chloroform, and it was made basic with saturated aqueous sodium bicarbonate. Thereafter, the organic layer was washed using saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 10/1) and the title compound was obtained as a straw-coloured solid.

¹H-NMR(CDCl₃) δ : 1.60-2.60 (6H, m), 2.80-3.05 (1H, m), 3.10-4.00 (4H, m), 5.20-5.60 (1H, m), 6.95-7.70 (11H, m), 7.75-7.95 (1H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 522 (M+H).

Example 499**6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,3,4]-oxadiazol-2-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 6-(5-methyl-[1,3,4]-oxadiazol-2-yl) pyridin-3-ol, the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.40-2.40 (7H, m), 2.50-2.80 (3H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.00 (1H, m), 8.05-8.30 (1H, m), 8.30-8.50 (1H, m), 8.50-8.80 (2H, m), 10.50-11.00(1H, m).

ESI-MS (m/e): 482 (M+H).

Example 500**6-(1-acetyl pyrrolidin-2-yl)-5-((6-([1,3,4]-oxadiazol-2-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 6-([1,3,4]-oxadiazol-2-yl) pyridin-3-ol, the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.40-2.40 (7H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.00 (1H, m), 8.05-8.80 (5H, m), 10.50-11.00 (1H, m).

ESI-MS (m/e): 468 (M+H).

Example 5016-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-(4-pyrimidin-2-yl phenoxy)-1H-benzimidazole

Using 4-pyrimidin-2-yl phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.90 and 2.13 (total 3H, each s), 1.94-2.53 (4H, m), 3.62-3.80 (1H, m), 3.80-4.00 (1H, m), 5.38-5.46 (1H, m), 7.16-7.56 (6H, m), 7.95-8.04 (1H, m), 8.24-8.33 (1H, m), 8.46 (2H, d, J = 9.0 Hz), 8.70-8.79 (1H, m), 8.83-8.85 (2H, m).

ESI-MS (m/e): 477 (M+H).

Example 5021-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methyl) pyrrolidine-2,5-dione

Using 1-((5-hydroxypyridin-2-yl) methyl) pyrrolidine-2,5-dione, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.46 (7H, m), 2.74-2.86 (4H, m), 3.53-3.90 (2H, m), 4.76-4.87 (2H, m), 5.18-5.48 (1H, m), 6.76-7.67 (5H, m), 7.80-7.91 (1H, m), 8.28-8.44 (2H, m), 8.57-8.67 (1H, m), 11.07-11.41 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 5036-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-((6-(5-(trifluoromethyl) -[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-1H-benzimidazole

Using 6-(5-(trifluoromethyl)-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.89-2.54 (7H, m), 3.84-4.01 (2H, m), 5.32-5.42 (1H, m), 7.20-7.80 (4H, m), 7.98-8.03 (1H, m), 8.24-8.37 (2H, m), 8.60-8.65 (1H, m), 8.73-8.80 (1H, m).

ESI-MS (m/e): 536 (M+H).

Example 5046-(1-acetyl pyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H,

m), 7.80-8.50 (3H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 434 (M+H).

Example 505

6-(1-acetyl pyrrolidin-2-yl)-5-((6-bromopyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-bromopyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H, m), 7.70-8.00 (1H, m), 8.05-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 478, 480 (M+H).

Example 506

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methoxypyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methoxypyridin-3-ol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-4.10 (5H, m), 5.10-5.70 (1H, m), 6.60-7.70 (5H, m), 7.70-7.95 (1H, m), 7.95-8.10 (1H, m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 430 (M+H).

Example 507

5-((2'-fluorobiphenyl-4-yl) oxy)-6-(1-(methanesulphonyl) pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazole

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 498 (Step 7), the title compound was obtained as colourless oil substance by the same process as in Example 178, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 2.70-3.00 (3H, m), 3.40-3.80 (2H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 529 (M+H).

Example 508

Methyl 2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxylate

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole

obtained in Example 498 (Step 7), the title compound was obtained as a colourless oily substance by the same process as in Example 181, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 3.40-3.80 (5H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.8 (1H, m).

ESI-MS (m/e): 509 (M+H).

Example 509

2-(5-((2'-fluorobiphenyl-4-yl)

oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)-N,N-dimethylpyrrolidine-1-carboxamide

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 498 (Step 7), the title compound was obtained as a white solid in accordance with Example 336 (Step 1) (Step 2), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CDCl₃) δ : 1.60-2.20 (3H, m), 2.20-2.50 (1H, m), 2.72 (3H, s), 2.84 (3H, s), 3.40-3.80 (2H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 522 (M+H).

Example 510

1-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl)

methyl) pyrrolidin-2-one

Using 1-((5-hydroxypyridin-2-yl) methyl) pyrrolidin-2-one, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.57 (11H, m), 3.33-3.89 (4H, m), 4.48-4.64 (2H, m), 5.20-5.51 (1H, m), 6.77-7.67 (5H, m), 7.77-7.90 (1H, m), 8.27-8.42 (2H, m), 8.56-8.66 (1H, m), 11.16-11.53 (1H, m).

ESI-MS (m/e): 497 (M+H).

Example 511

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(3-methyl-1H-[1,2,4]-triazol-5-yl)

phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(3-methyl-1H-[1,2,4]-triazol-5-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.76-2.82 (10H, m), 3.50-3.90 (2H, m), 5.13-5.59 (1H, m), 6.64-8.04 (8H, m), 8.23-8.64 (2H, m).

ESI-MS (m/e): 480 (M+H).

Example 512

6-(1-(difluoro acetyl) pyrrolidin -2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using difluoro acetic acid, the title compound was obtained as a white solid in accordance with Example 498 (Step 8), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.50 (4H, m), 3.60-4.20 (2H, m), 5.20-6.20 (2H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 529 (M+H).

Example 513

2-2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl acetate

Using acetoxy acetic acid, the title compound was obtained as a yellow oily substance in accordance with Example 498 (Step 8), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.40 (7H, m), 3.40-4.00 (2H, m), 4.05-4.80 (2H, m), 5.10-5.60 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 551 (M+H).

Example 514

(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methanol

To tetrahydrofuran 2 ml solution of ethyl 5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridine-2-carboxylate 90 mg obtained in Example 495 was added lithium aluminium hydride 20 mg under ice cooling, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with chloroform, washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

¹H-NMR(CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 4.70-4.85 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H, m), 7.70-7.95 (1H, m), 8.30-8.50 (2H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 430 (M+H).

Example 515

2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl)-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol

To methanol solution 0.5 ml of 2-(2-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl)-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl acetate 11 mg obtained in Example 513 was added potassium carbonate 10 mg, and the reaction liquor was stirred at room temperature for one day. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 1.40-2.50 (4H, m), 3.40-4.20 (4H, m), 5.05-5.70 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 509 (M+H).

Example 516

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(fluoromethyl) pyridin-3-yl) oxy)-2-pyridin-2-yl)-1H-benzimidazole

To chloroform 1 ml solution of (5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl)-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methanol 17 mg obtained in Example 514, bis (2-methoxyethyl) amino sulphur tri fluoride 0.050 ml was added under ice cooling, and the reaction liquor was stirred at 0°C for two hours. The reaction liquor was diluted with chloroform, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under the reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as slight yellow solid.

¹H-NMR (CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.60 (3H, m), 6.80-7.70 (5H, m), 7.70-7.95 (1H, m), 8.30-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 432 (M+H).

Example 517

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(3-methyl-[1,2,4]-oxadiazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl)-1H-benzimidazole

Using 6-(3-methyl [1,2,4]-oxadiazol-5-yl) pyridin-3-ol, the title compound was obtained as an

oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.65-2.57 (10H, m), 3.48-3.93 (5H, m), 5.17-5.52 (1H, m), 6.82-7.67 (7H, m), 7.80-7.91 (1H, m), 8.34-8.44 (1H, m), 8.57-8.67 (1H, m), 11.32-11.68 (1H, m).

ESI-MS (m/e): 482 (M+H).

Example 518

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1-methyl-1H-tetrazol-5-yl)phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1-methyl-1H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same method as in Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.83-2.40 (7H, m), 3.58-3.90 (2H, m), 4.15 and 4.19 (total 3H, each s), 5.16-5.48 (1H, m), 6.93-7.78 (7H, m), 7.80-7.91 (1H, m), 8.34-8.42 (1H, m), 8.56-8.65 (1H, m).

ESI-MS (m/e): 481 (M+H).

Example 519

5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)-N-methylpyridine-2-carboxamide

Using 5-hydroxy-N-methylpyridine-2-carboxamide, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.50 (7H, m), 2.90-3.10 (3H, m), 3.50-4.00 (2H, m), 5.05-5.50 (1H, m), 6.80-7.70 (3H, m), 7.70-8.00 (2H, m), 8.10-8.50 (3H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 457 (M+H).

Example 520

3-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)pyridin-2-yl)-1,3-oxazolidin-2-one

Using 3-(5-hydroxypyridin-2-yl)-1,3-oxazolidin-2-one, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.50 (7H, m), 3.50-4.00 (2H, m), 4.10-4.35 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (4H, m), 7.70-8.00 (1H, m), 8.10-8.50 (3H, m), 8.50-8.70 (1H, m), 10.70-11.10 (1H, m).

ESI-MS (m/e): 485 (M+H).

Example 521

6-(1-acetyl pyrrolidin-2-yl)-5-(6-methylpyridin-3-yl sulphanyl)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridine-3-thiol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.20-2.50 (10H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.00 (6H, m), 8.20-8.70 (3H, m).

ESI-MS (m/e): 430 (M+H).

Example 5225-(((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) nicotinic acid methyl ester

Using 5-hydroxy nicotinic acid methyl ester, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.89 and 2.14 (total 3H, each s), 1.96-2.20 (3H, m), 2.32-2.54 (11H, m), 3.63-3.90 (2H, m), 3.93 (3H, s), 5.37-5.41 (1H, m), 7.20-7.57 (3H, m), 7.92-8.03 (2H, m), 8.30 (1H, t, J = 8.4 Hz), 8.65-8.67 (1H, m), 8.74-8.78 (1H, m), 8.89-8.92 (1H, m).

ESI-MS (m/e): 458 (M+H).

Example 5236-(1-acetyl pyrrolidin-2-yl)-5-(((6-(methylthio) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylthio pyridin-3-ol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.70 (10H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.10 (6H, m), 8.20-8.50 (2H, m), 8.50-8.70 (1H, m), 10.70-11.10 (1H, m).

ESI-MS (m/e): 446 (M+H).

Example 5246-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,3-dimethyl-1H-[1,2,4]-triazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,3-dimethyl-1H-[1,2,4]-triazol-5-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.79-2.2.53 (10H, m), 3.50-3.90 (5H, m), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m), 10.82-11.08 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 525

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,5-dimethyl-1H-[1,2,4]-triazol-3-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,5-dimethyl-1H-[1,2,4]-triazol-3-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.79-2.53 (10H, m), 3.50-3.90 (5H, in), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m), 10.82-11.08 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 526

6-(1-acetyl pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained in Example 338 (Step 2), pyrazine-2-carboxylic acid and 2'-fluorobiphenyl-4-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 3), (Step 5), a process based on these or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.20-2.50 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.80 (10H, m), 8.50-8.90 (2H, m), 9.40-10.00 (1H, m), 10.50-11.20 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 527

6-(1-acetyl pyrrolidin-2-yl)-5-((5-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 5-chloro-3-pyridinol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.89 and 2.15 (total 3H, each s), 1.94-2.20 (3H, m), 2.29-2.49 (1H, m), 3.62-3.97 (2H, m), 5.32-5.40 (1H, m), 7.17-7.63 (4H, m), 7.94-8.04 (1H, m), 8.26-8.41 (3H, m), 8.73-8.79 (1H, m).

ESI-MS (m/e): 434 (M+H).

Example 528

1-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) pyrrolidin-2-one

Using 1-(5-hydroxypyridin-2-yl) pyrrolidin-2-one, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of

these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.79-2.43 (9H, m), 2.58-2.71 (2H, m), 3.53-3.89 (2H, m), 3.98-4.17 (2H, m), 5.21-5.57 (1H, m), 6.77-7.57 (4H, m), 7.74-8.66 (5H, m).

ESI-MS (m/e): 483 (M+H).

Example 529

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.60 (10H, m), 3.50-3.95 (2H, m), 5.20-5.60 (1H, m), 6.65-7.80 (4H, m), 8.20-8.40 (1H, m), 8.50-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.40 (1H, m).

ESI-MS (m/e): 415 (M+H).

Example 530

6-(1-acetyl pyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl] pyridin-3-yl)

oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-[[1,2,4]-oxadiazol-3-yl] pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.43 (7H, m), 3.57-3.92 (2H, m), 5.19-5.46 (1H, m), 6.98-8.43 (7H, m), 8.55-8.87 (3H, m), 10.53-10.74 (1H, m).

ESI-MS (m/e): 468 (M+H).

Example 531

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,3-oxazol-4-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,3-oxazol-4-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.89-2.20 (6H, m), 2.28-2.50 (1H, m), 3.62-4.00 (2H, m), 5.39-5.50 (1H, m), 7.12-7.53 (5H, m), 7.80-7.89 (2H, m), 7.93-8.04 (1H, m), 8.24-8.33 (3H, m), 8.70-8.79 (1H, m).

ESI-MS (m/e): 466 (M+H).

Example 532

6-(1-acetyl pyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 526, a process based on this or a combination of these with a conventional procedure.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.20-5.60 (1H, m), 6.65-8.30 (5H, m), 8.40-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.60 (1H, m).

ESI-MS (m/e): 435 ($M+H$).

Example 533

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

$^1\text{H-NMR}$ (CD_3OD) δ : 1.90-2.19 (6H, m), 2.27-2.51 (1H, m), 3.61-4.00 (2H, m), 4.43 and 4.44 (total 3H, each s), 5.38-5.46 (1H, m), 7.23 (2H, d, $J = 8.6$ Hz), 7.24-7.60 (2H, m), 8.11-8.19 (2H, m), 8.67-8.70 (1H, m), 8.77 (1H, brs), 9.46 (1H, d, $J = 8.6$ Hz).

ESI-MS (m/e): 482 ($M+H$).

Example 534

6-(1-acetyl pyrrolidin-2-yl)-5-((6-bromopyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-bromopyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60-2.50 (7H, m), 3.60-3.95 (2H, m), 5.20-5.50 (1H, m), 6.80-8.40 (5H, m), 8.50-8.80 (2H, m), 9.50-9.70 (1H, m), 10.40-11.10 (1H, m).

ESI-MS (m/e): 479,481 ($M+H$).

Example 535

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol enantiomer A and enantiomer B

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl)

phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer B 10 mg obtained in Example 493 was optically resolved with column for optical resolution (CHIRALPAK AD 2 $\text{cm}\phi$ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 40/60/0.1, flow rate: 10 mL/min), and enantiomer A (retention time : 10.5 min) and enantiomer B (retention time : 19.0 min) were respectively obtained as white solid.

Enantiomer A

ESI-MS (m/e): 495 ($M+H$).

Enantiomer B

ESI-MS (m/e): 495 ($M+H$).

Example 536

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.88 and 2.02 (total 3H, each s), 1.93-2.20 (3H, m), 2.28-2.50 (1H, m), 3.60-4.00 (2H, m), 4.47 and 4.48 (total 3H, each s), 5.32-5.42 (1H, m), 7.22-7.70 (4H, m), 7.95-8.02 (1H, m), 8.25-8.32 (2H, m), 8.61-8.64 (1H, m), 8.73 (1H, brs).

ESI-MS (m/e): 482 (M+H).

Example 537

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.91 and 2.16 (total 3H, each s), 2.00-2.20 (3H, m), 2.38-2.55 (1H, m), 3.63-4.01 (2H, m), 4.50 and 4.51 (total 3H, each s), 5.35-5.44 (1H, m), 7.33-7.60 (2H, m), 7.66-7.73 (1H, m), 8.27-8.34 (1H, m), 8.65-8.67 (1H, m), 8.71-8.73 (1H, m), 8.78-8.80 (1H, m), 9.48-9.50 (1H, m).

ESI-MS (m/e): 483 (M+H).

Example 538

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.91-2.20 (6H, m), 2.33-2.52 (1H, m), 3.60-4.00 (2H, m), 4.48-4.90 (3H, m), 5.37-5.44 (1H, m), 7.22-7.68 (4H, m), 7.97-8.04 (1H, m), 8.19-8.23 (1H, m), 8.25-8.31 (1H, m), 8.55-8.59 (1H, m), 8.74 (1H, brs).

ESI-MS (m/e): 482 (M+H).

Example 539

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-1H-tetrazol-1-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(5-methyl-1H-tetrazol-1-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.91 and 2.16 (total 3H, each s), 1.96-2.20 (3H, m), 2.33-2.54 (1H, m), 2.63 and 2.64 (total 3H, each s), 3.64-4.00 (2H, m), 5.38-5.43 (1H, m), 7.32-7.57 (4H, m), 7.61-7.68 (2H, m), 8.70-8.73 (1H, m), 8.78-8.80 (1H, m), 9.47-9.49 (1H, 1).
ESI-MS (m/e): 482 (M+H).

Example 540

6-(1-acetyl pyrrolidin-2-yl)-5-((6-[1H-pyrazol-1-yl] pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(1H-pyrazol-1-yl) pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.67-2.48 (7H, m), 3.50-3.92 (2H, m), 5.14-5.57 (1H, m), 6.41-6.50 (1H, m), 6.80-8.03 (7H, m), 8.17-8.67 (4H, m), 11.00-11.11.27 (1H, m).
ESI-MS (m/e): 466 (M+H).

Example 541

6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-((6-[1H-[1,2,4]-triazol-1-yl] pyridin-3-yl) oxy)-1H-benzimidazole

Using 6-(1H-[1,2,4]-triazol-1-yl) pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.62-2.45 (7H, m), 3.52-3.90 (2H, m), 5.20-5.55 (1H, m), 6.79-8.68 (10H, m), 9.02-9.13 (1H, m), 11.17-11.52 (1H, m).
ESI-MS (m/e): 467 (M+H).

Example 542

5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer A and enantiomer B

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole 59.0 mg obtained by the same processes as in Example 162 (Step 2)-(Step 7) was optically resolved with column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: ethanol / 2-propanol / diethylamine 25/75/0.1, flow rate: 12-18 ml/min), and enantiomer A and enantiomer B were respectively obtained as pale yellow solid. (retention time : enantiomer A 13.5 min, enantiomer B 30.8 min, CHIRALPAK AD 4.6 mmφ x 250 cmL (made by Daicel Chemicals

Co.), mobile phase: ethanol / 2-propanol / diethylamine 25/75/0.1, flow rate: 1 ml/min).

Example 543

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)

phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

To 5-(4-(2-methyl-2H-tetrazol-5-yl)

phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer A 24.7 mg obtained in Example 542 dissolved in chloroform 1 ml was added anhydrous acetic acid 0.006 ml, and the reaction liquor was stirred at room temperature for ten minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

¹H-NMR(CD₃OD) δ : 1.90-2.20 (6H, m), 2.24-2.49 (1H, m), 3.66-4.00 (2H, m), 5.37-5.46 (1H, m), 7.12-7.60 (5H, m), 7.94-8.04 (1H, m), 8.04-8.20 (2H, m), 8.29 (1H, t, J = 8.2 Hz), 8.68-8.78 (1H, m).

ESI-MS (m/e): 481 (M+H).

Example 544

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)

phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

To chloroform 1 ml solution of 5-(4-(2-methyl-2H-tetrazol-5-yl)

phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer B 30.9 mg obtained in Example 542 was added acetic anhydride 0.007 ml, and thereafter, the reaction liquor was stirred at room temperature for 10 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

ESI-MS (m/e): 481 (M+H).

Example 545

5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl)

phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A, B, C and D

Using 5-methyl dihydrofuran-2(3H)-one, 4-component mixture of the title compound was obtained by a process same as Example 485, process based on this or combining these with the normal method. The obtained 4-component mixture 15 mg was column for optically resolution (CHIRAL-CEL OD-H 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane/ethanol diethylamine = 80/20/0.1), and enantiomer A (retention time : 13.67 min), enantiomer B

(retention time : 15.24 min), enantiomer C (retention time : 18.96 min) and enantiomer D (retention time : 22.90 min) were respectively obtained as pale yellow solid.

Enantiomer A

¹H-NMR (CDCl₃) δ : 1.23-1.38 (3H, m), 1.50-2.57 (7H, m), 3.04 and 3.08 (3H, s), 4.24-4.60 (1H, m), 5.18-5.43 (1H, m), 6.92-7.83 (5H, m), 7.83-7.98 (3H, m), 8.34-8.43 (1H, m), 8.60-8.67 (1H, m), 10.84-11.33 (1H, m).

ESI-MS (m/e): 491 (M+H).

Enantiomer B

¹H-NMR (CDCl₃) δ : 1.22-2.20 (9H, m), 2.23-2.45 (1H, m), 3.04 and 3.08 (3H, s), 4.10-4.22 (1H, m), 5.09-5.23 (1H, m), 7.04-7.70 (5H, m), 7.83-7.97 (3H, m), 8.34-8.48 (1H, m), 8.61-8.69 (1H, m), 10.73-11.16 (1H, m).

ESI-MS (m/e): 491 (M+H).

Enantiomer C

ESI-MS (m/e): 491 (M+H).

Enantiomer D.

ESI-MS (m/e): 491 (M+H).

Example 546

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 526, a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.88-2.20 (6H, m), 2.21-2.31 (1H, m), 3.61-4.00 (2H, m), 4.46 and 4.47 (total 3H, each s), 5.34-5.44 (1H, m), 7.22-7.71 (3H, m), 8.18-8.25 (1H, m), 8.50-8.60 (1H, m), 8.65-8.70 (1H, m), 8.72-8.80 (1H, m), 9.44-9.47 (1H, m).

ESI-MS (m/e): 483 (M+H).

Example 547

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-(methoxymethyl)-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-(methoxymethyl)-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

$^1\text{H-NMR}(\text{CD}_3\text{OD}) \delta$: 1.90-2.20 (6H, m), 2.22-2.71 (1H, m), 3.53 (3H, s), 5.38-5.46 (1H, m), 5.96 and 5.97 (total 3H, each s), 7.20-7.56 (5H, m), 7.95-8.03 (1H, m), 8.17-8.22 (2H, m), 8.29 (1H, t, $J = 8.0$ Hz), 8.73-8.79 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 548

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(methoxymethyl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.60-2.43 (7H, m), 3.34-3.91 (5H, m), 4.45-4.59 (2H, m), 5.20-5.52 (1H, m), 6.86-7.67 (5H, m), 7.80-7.90 (1H, m), 8.29-8.48 (2H, m), 8.55-8.67 (1H, m), 10.87-11.27 (1H, m).

ESI-MS (m/e): 444 (M+H).

Example 549

2-(2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure using 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same processes as in Example 162 (Step 2)-(Step 7).

$^1\text{H-NMR}(\text{CD}_3\text{OD}) \delta$: 1.94-2.16 (3H, m), 2.23-2.48 (1H, m), 3.57-4.34 (4H, m), 4.43 and 4.44 (total 3H, each s), 5.27-5.52 (1H, m), 7.17-7.57 (5H, m), 7.94-8.04 (1H, m), 8.09-8.20 (2H, m), 8.24-8.32 (1H, m), 8.69-8.81 (1H, m).

ESI-MS (m/e): 497 (M+H).

Example 550

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide diastereomer B obtained in Example 493 and 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure..

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.82-2.43 (5H, m), 2.68 and 2.70 (3H, s), 3.64-4.40 (2H, m), 5.19-5.40 (1H, m), 5.42-5.64 (1H, m), 7.02-7.79 (4H, m), 7.80-7.92 (1H, m), 8.00-8.12 (1H, m), 8.35-8.42 (1H,

m), 8.60-8.75 (2H, m), 10.50-10.68 (1H, m).

ESI-MS (m/e): 500 (M+H).

Example 551

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-ethyl-2H-tetrazol-5-yl)
phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-ethyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.68 (3H, t, J = 7.2 Hz), 1.90 and 2.13 (total 3H, each s), 1.97-2.20 (3H, m), 2.29-2.53 (1H, m), 3.62-4.00 (2H, m), 4.73-7.79 (2H, m), 5.37-5.47 (1H, m), 7.19-7.60 (5H, m), 7.93-8.03 (1H, m), 8.10-8.20 (2H, m), 8.23-8.33 (1H, m), 8.74 (1H, brs)

ESI-MS (m/e): 495 (M+H).

Example 552

2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)
pyrrolidine-1-carboxamide

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 184, a process based on this or a combination of these with a normal procedure using 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same process as in Example 162 (Step 2)-(Step 7).

¹H-NMR(CD₃OD) δ : 1.97-2.10 (3H, m), 2.28-2.41 (1H, m), 3.52-3.63 (1H, m), 3.74-3.62 (1H, m), 5.26-5.41 (1H, m), 7.10-7.33 (1H, m), 7.23 (2H, d, J = 8.8 Hz), 7.44-7.61 (2H, m), 7.95-7.99 (1H, m), 8.12 (2H, d, J = 8.8 Hz), 8.27 (1H, d, J = 8.2 Hz), 8.72-8.73 (1H, m).

ESI-MS (m/e): 482 (M+H).

Example 553

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)
phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 550, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.83-2.17 (total 3H, each s), 2.10-2.40 (2H, m), 3.62-4.21 (2H, m), 4.41 and 4.42 (total 3H, each s), 5.23-5.43 (1H, m), 5.46-5.73 (1H, m), 7.10-7.65 (5H, m), 7.94-8.02 (1H, m), 8.03-8.17 (2H, m), 8.27 (1H, t, J = 8.8 Hz), 8.72 (1H, brs).

ESI-MS (m/e): 499 (M+H).

Example 554

5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridine-2-one enantiomer A and enantiomer B

Using 5'-hydroxy-2H-1,2'-bipyridin-2-one,

5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one 15.0 mg obtained by the same process as in Example 162 (Step 2)-(Step 7) was optically resolved with column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: 2-propanol, flow rate: 10 ml/min), and enantiomer A (retention time: 23.6 min), enantiomer B (retention time: 50.7 min) were respectively obtained as pale yellow solid.

Example 555

5'-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer A

To 5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer A 6.5mg obtained in Example 554 dissolved in chloroform 1 ml was added acetic anhydride 0.003 ml, and thereafter the reaction liquor was stirred at room temperature for 30 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

¹H-NMR(CD₃OD) δ : 1.91 and 2.16 (total 3H, each s), 1.94-2.20 (3H, m), 2.32-2.52 (1H, m), 3.63-3.98 (2H, m), 5.38-5.44 (1H, m), 6.49-6.54 (1H, m), 6.63-6.68 (1H, m), 7.23-7.58 (3H, m), 7.60-7.67 (2H, m), 7.77 (1H, dd, J = 8.8, 15.8 Hz), 7.87-7.93 (1H, m), 7.95-8.01 (1H, m), 8.27-8.31 (1H, m), 8.41 (1H, d, J = 2.9 Hz), 8.73 (1H, t, J = 4.7 Hz)
ESI-MS (m/e): 493 (M+H).

Example 556

5'-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer B

To chloroform 1 ml solution of 5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer B 5.8 mg obtained in Example 554, acetic anhydride 0.003 ml was added, and thereafter the reaction liquor was stirred at room temperature for 30 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

ESI-MS (m/e): 493 (M+H).

Example 557

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using

cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.80-2.84 (2H, m), 1.94 and 2.25 (total 3H, each s), 3.90-4.30 (2H, m), 4.43 (3H, s), 5.28-5.50 (1H, m), 5.51-5.59 (1H, m), 7.18-7.64 (5H, m), 7.94-8.01 (1H, m), 8.12-8.18 (2H, m), 8.25-8.29 (1H, m), 8.70-8.77 (1H, m).

ESI-MS (m/e): 499 (M+H).

Example 558

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one, the title compound was obtained as yellow oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.20-2.50 (7H, m), 3.50-4.00 (2H, m), 3.90-4.25 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (7H, m), 7.80-8.00 (1H, m), 8.25-8.50 (1H, m), 8.50-8.80 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 484 (M+H).

Example 559

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.72-2.59 (10H, m), 3.53-3.90 (2H, m), 5.20-5.55 (1H, m), 6.81-7.66 (5H, m), 7.78-7.92 (1H, m), 8.28-8.43 (2H, m), 8.55-8.66 (1H, m), 11.07-11.55 (1H, m).

ESI-MS (m/e): 414 (M+H).

Example 560

6-(1-acetyl pyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-pyrazin-2-yl pyridin-3-ol, the title compound was obtained as a yellow oily substance by the same process as in Example 483, a process based on this or a combination of these with a

normal procedure.

¹H-NMR (CDCl₃) δ : 0.80-2.40 (7H, m), 3.60-3.90 (2H, m), 5.20-5.60 (1H, m), 7.00-7.80 (4H, m), 7.80-8.00 (1H, m), 8.30-8.50 (2H, m), 8.50-8.80 (4H, m), 9.50-9.70 (1H, m), 10.40-10.80 (1H, m).

ESI-MS (m/e): 478 (M+H).

Example 561

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole

Using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 2'-fluorobiphenyl-4-ol, the title compound was obtained as a yellow oily substance in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 0.80-2.80 (6H, m), 3.80-4.40 (2H, m), 5.05-5.50 (1H, m), 7.00-7.70 (11H, m), 7.75-7.95 (1H, m), 8.30-8.50 (1H, m), 8.50-8.75 (1H, m), 10.60-10.80 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 562

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-(4-pyrazin-2-ylphenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 4-pyrazin-2-yl phenol, the title compound was obtained as yellow oily substance in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.20-2.80 (6H, m), 3.80-4.40 (2H, m), 5.20-5.50 (1H, m), 7.00-7.70 (5H, m), 7.80-7.95 (1H, m), 7.95-8.20 (2H, m), 8.30-8.50 (2H, m), 8.50-8.80 (2H, m), 8.95-9.20 (1H, m), 10.60-10.80 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 563

N-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)pyridin-2-yl)methyl)acetamide

Using N-((5-hydroxypyridin-2-yl)methyl)acetamide, the title compound was obtained as oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.83-2.47 (10H, m), 3.54-3.90 (2H, m), 4.48-4.59 (2H, m), 5.21-5.50 (1H, m), 6.66-7.69 (6H, m), 7.79-7.91 (1H, m), 8.30-8.44 (2H, m), 8.54-8.69 (1H, m), 10.96-11.29 (1H, m).

ESI-MS (m/e): 471 (M+H).

Example 564

6-(1-acetyl pyrrolidin-2-yl)-5-((6-fluoropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-fluoropyridin-3-ol, the title compound was obtained as yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.40-2.50 (7H, m), 3.50-4.00 (2H, m), 5.00-5.60 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.00-8.15 (1H, m), 8.25-8.50 (1H, m), 8.50-8.70 (1H, m), 10.60-10.80 (1H, m).

ESI-MS(m/e): 418[M+H].

Example 565

Cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

Step 1

Synthesis of cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

In accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure, the title compound was obtained using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 6-cyano-pyridin-3-ol.

Step 2

Production of

cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

Using cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone of racemic body obtained in (Step 1), the title compound was respectively obtained by the same process as in Example 333, a process based on this or a combination of these with a normal procedure.

Enantiomer A.

¹H-NMR(CD₃OD) δ : 1.91 (3H x 1/2, s), 2.22 (3H x 1/2, s), 2.32-2.67 (2H, m), 3.95-4.30 (2H, m), 5.27-5.47 (2H, m), 7.35-7.64 (3H, m), 7.85-7.92 (1H, m), 7.97-7.99 (1H, m), 8.29 (1H, t, J = 7.6 Hz), 8.60 (1H, d, J = 3.1 Hz), 8.74 (1H, s).

ESI-MS (m/e): 443 (M+H).

Enantiomer B.

ESI-MS (m/e): 443 (M+H).

Example 566

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)
oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Step 1

Synthesis of N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)
pyridine-2-carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide diastereomer B300 mg obtained in Example 493 was optically resolved with column for optical resolution (CHIRAL CEL OD 2 cm ϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 50/50/0.1, flow rate: 10 ml/min), and enantiomer A and enantiomer were respectively obtained as yellow solid.

Step 2

Production of 6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)
oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer A and 2'-fluorobiphenyl-4-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.82-2.43 (5H, m), 3.63-4.36 (2H, m), 5.25-5.70 (2H, m), 7.07-7.58 (11H, m), 7.74-7.90 (1H, m), 8.35-8.43 (1H, m), 8.58-8.68 (1H, m), 10.37-10.60 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 567

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)
oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 566 (Step 1), the title compound was obtained in accordance with Example 566 (Step 2), a process based on this or a combination of these with a conventional procedure.

ESI-MS(m/e): 511 (M+H).

Example 568

Cis-1-(4-fluoro-2-(6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-ethanesulfonyl-phenol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.90 (3H x 0.5, s), 2.22 (3H x 0.5, s), 2.25-2.75 (2H, m), 3.88-4.39 (2H, m), 5.24-5.48 (2H, m), 7.23-7.75 (5H, m), 7.90-8.02 (3H, m), 8.27-8.30 (1H, m), 8.73-8.75 (1H, m).
ESI-MS (m/e): 509 (M+H).

Example 569

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl)-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidine-2-one enantiomer A

Step 1

Synthesis of t-butyl 2-(2-fluoro-4-((pyrazine-2-ylcarbonyl) amino) phenyl) pyrrolidine-1-carboxylate

In 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 3 g obtained in Example 338 (Step 2) dissolved in pyridine 5 ml were added successively pyrazine-2-carboxylic acid 1.5 g, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 3.1 g, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as a yellow oily substance.

Step 2

Synthesis of N-(3-fluoro-4-pyrrolidin-2-yl phenyl) pyrazine-2-carboxamide dihydrochloride

To methanol 50 ml solution of t-butyl 2-(2-fluoro-4-((pyrazin-2-yl carbonyl) amino) phenyl) pyrrolidine-1-carboxylate 4.4 g was added 4 N hydrochloric acid-dioxane solution 50 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow solid

Step 3

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide

To N-(3-fluoro-4-pyrrolidin-2-yl phenyl) pyrazine-2-carboxamide dihydrochloride 4.3 g dissolved in pyridine 50 ml solution, acetic anhydride 1.5 ml was added, and the reaction liquor was stirred at room temperature for 20 minutes. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter

dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 50/1) and the title compound was obtained as a yellow solid

Step 4

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide

Fuming nitric acid 40 ml was added to N-(4-(1-acetyl pyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide 3.9 g under ice cooling, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was diluted with iced water, and it was made basic with saturated aqueous sodium bicarbonate, thereafter, extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as a yellow oily substance.

Step 5

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide 500 mg was optically resolved with column for optical resolution (CHIRALPAK OD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / 2-propanol 1/1, flow rate: 15 ml/min), and enantiomer A (retention time: 18 min), enantiomer B (retention time: 25 min) were respectively obtained as pale yellow oily substance.

Step 6

Production of 3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidine-2-one enantiomer A

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one and N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer A, the title compound, one of chiral body was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.00-2.40 (7H, m), 3.50-3.90 (2H, m), 3.90-4.20 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (6H, m), 8.50-8.75 (2H, m), 9.50-9.70 (1H, m), 10.30-10.60 (1H, m).

ESI-MS (m/e): 485 (M+H).

Example 570

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one enantiomer B

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one and N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer B obtained in Example 569 (step 5), the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure. ESI-MS (m/e): 485 (M+H).

Example 571

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(cyclopropyl sulfonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(cyclopropyl sulfonyl) phenol, the title compound was obtained as slight yellow solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 0.90-1.20 (2H, m), 1.20-1.40 (3H, m), 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.50 (1H, m), 7.00-8.20 (8H, m), 8.30-8.50 (1H, m), 8.55-8.80 (1H, m), 10.70-11.20 (1H, m).

ESI-MS(m/e): 503 (M+H).

Example 572

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methanesulfonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(ethanesulfonyl) phenol, the title compound was obtained as a white solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.20-1.40 (3H, m), 1.60-2.50 (7H, m), 3.00-3.20 (2H, m), 3.50-4.00 (2H, m), 5.10-5.50 (1H, m), 6.90-7.80 (5H, m), 7.80-8.00 (3H, m), 8.30-8.50 (1H, m), 8.50-8.75 (1H, m), 10.60-11.20 (1H, m).

ESI-MS (m/e): 491 (M+H).

Example 573

Cis-1-(4-fluoro-2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.20-1.40 (3H, m), 1.90-2.30 (3H, m), 2.00-2.80 (2H, m), 3.20-3.50 (2H, m), 3.84-4.25 (2H, m), 5.27-5.45 (2H, m), 7.40-7.80 (4H, m), 8.00-8.20 (2H, m), 8.24-8.40 (1H,

m), 8.66 (1H, s), 8.80 (1H, brs).

ESI-MS (m/e): 510 (M+H).

Example 574

Cis-1-(4-fluoro-2-(6-(6-(5-methyl-[1,2,4]-oxadiazol-3-yl)

pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.90-2.30 (3H, m), 2.00-2.80 (2H, m), 2.75 (3H, s), 3.84-4.40 (2H, m), 5.30-5.45 (2H, m), 7.25-7.80 (4H, m), -7.90-8.40 (3H, m), 8.55-8.68 (1H, m), 8.75 (1H, s).

ESI-MS (m/e): 500 (M+H).

Example 575

5-((6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)

pyridine-2-carbonitrile

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 566 (Step 1) and 5-hydroxypyridine-2-carbonitrile, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.54-2.45 (5H, m), 3.61-4.34 (2H, m), 5.09-5.54 (2H, m), 7.01-7.95 (6H, m), 8.34-8.47 (1H, m), 8.54-8.73 (2H, m), 10.66-10.79 (1H, m).

ESI-MS (m/e): 443 (M+H).

Example 576

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)

oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.54-2.45 (5H, m), 3.61-4.34 (2H, m), 5.09-5.54 (2H, m), 7.01-7.95 (6H, m), 8.34-8.47 (1H, m), 8.54-8.73 (2H, m), 10.66-10.79 (1H, m).

ESI-MS (m/e): 443 (M+H).

Example 577

6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl)

oxy)-1H-benzimidazole

Using 6-pyrazin-2-yl pyridin-3-ol, the title compound was obtained as a straw-coloured oily

substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.05-2.50 (7H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 7.00-7.80 (3H, m), 8.20-8.45 (1H, m), 8.45-8.80 (5H, m), 9.50-9.70 (2H, m), 10.40-11.30 (1H, m).

ESI-MS (m/e): 479 (M+H).

Example 578

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol and N-(4-(1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)pyridine-2-carboxamide obtained in Example 545, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.20-2.30 (7H, m), 2.30-2.70 (6H, m), 4.05-4.60 (1H, m), 5.20-5.60 (1H, m), 6.80-7.50 (4H, m), 7.70-7.90 (1H, m), 8.15-8.20 (1H, m), 8.25-8.40 (2H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 428 (M+H).

Example 579

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-chloropyridin-3-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 578, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.20-2.60 (10H, m), 4.05-4.65 (1H, m), 5.10-5.50 (1H, m), 6.80-7.70 (4H, m), 7.80-8.10 (2H, m), 8.15-8.50 (2H, m), 8.60-8.80 (1H, m), 10.80-11.30 (1H, m).

ESI-MS (m/e): 448 (M+H).

Example 580

2-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)pyridin-2-ylsulphanyl) ethanol

To N,N-dimethylformamide 1 ml solution of 6-(1-acetylpyrrolidin-2-yl)-5-((6-chloropyridin-3-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole 20 mg obtained in Example 504 were added successively 2-mercaptoethanol 20 mg and potassium carbonate 10 mg, and the reaction liquor was stirred at 120°C for five hours. After cooling, the reaction liquor was diluted using saturated aqueous sodium bicarbonate, extracted with chloroform, and the organic layer was dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was refined by preparative thin layer

chromatography (KieselgelTM60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound was obtained as a white solid

¹H-NMR (CDCl₃) δ : 1.10-2.50 (7H, m), 3.20-3.40 (2H, m), 3.50-4.00 (4H, m), 5.20-5.50 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.10-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-10.80 (1H, m).

ESI-MS (m/e): 476 (M+H).

Example 581

3-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl)-1H-benzimidazol-5-yl) oxy) pyridin-2-yl sulphanyl) propane-1-ol

Using 3-mercapto propane-1-ol, the title compound was obtained as a white solid by the same process as in Example 580, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.50 (7H, m), 3.20-3.40 (2H, m), 3.50-4.40 (6H, m), 5.20-5.60 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.20-8.50 (2H, m), 8.50-8.70 (1H, m), 10.80-11.20 (1H, 1).

ESI-MS (m/e): 490 (M+H).

Example 582

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-methyl picolinic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.86 and 2.10 (total 3H, each s), 1.92-2.43 (4H, m), 2.65 and 2.66 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.62-3.96 (2H, m), 5.25-5.32 (1H, m), 7.23 and 7.25 (total 2H, each d, J = 8.8 Hz), 7.20-7.58 (3H, m), 7.95 and 7.99 (total 2H, each d, J = 8.8 Hz), 8.38-8.42 (1H, m), 9.12-9.16 (1H, 1).

ESI-MS (m/e): 491 (M+H).

Example 583

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyrazine-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-methylpyrazine-2-carboxylic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.87-2.45 (7H, m), 2.66 and 2.67 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.63-4.00 (2H, m), 5.26-5.34 (1H, m), 7.20-7.61 (4H, m), 7.96 and 7.99 (total 2H, each d,

J = 8.8 Hz), 8.69 (1H, s), 9.32 and 9.34 (total 1H, each s).

ESI-MS (m/e): 492 (M+H).

Example 584

1-(4-((6-(1-acetyl-3-fluoropyridin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone

Using 1-(4-hydroxyphenyl) ethanone, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.62-2.60 (8H, m), 3.60-3.98, 4.04-4.33 (total 2H, each m), 5.11-5.56 (2H, m), 7.00-8.02 (8H, m), 8.33-8.48 (1H, m), 8.57-8.71 (1H, m), 10.76-11.09 (1H, m).

ESI-MS (m/e): 459 (M+H).

Example 585

6-(1-acetyl-3-fluoropyridin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.54-2.45 (5H, m), 3.60-4.35 (2H, m), 5.20-5.60 (2H, m), 6.90-7.00, 7.21-7.43, 7.60-7.93 (total 6H, eachm), 8.22-8.45 (2H, m), 8.58-8.70 (1H, m), 10.63-10.90 (1H, m).

ESI-MS (m/e): 452 (M+H).

Example 586

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.47 (7H, m), 2.57-2.73 (3H, m), 3.57-3.93 (2H, m), 5.21-5.48 (1H, m), 7.00-7.76 (3H, m), 7.96-8.14 (1H, m), 8.52-8.68 (3H, m), 9.54-9.65 (1H, m), 10.70-11.02, 11.53-10.66 (total 1H, each m).

ESI-MS (m/e): 483 (M+H).

Example 587

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(methanesulphonyl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(methanesulphonyl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.51-2.47 (7H, m), 3.14-3.27 (3H, m), 3.58-3.92 (2H, m), 5.14-5.40 (1H, m), 7.03-7.79 (4H, m), 7.95-8.11 (1H, m), 8.48-8.71 (2H, m), 9.56-9.66 (1H, m), 10.65-10.194, 11.34-11.49 (total 1H, each m).

ESI-MS (m/e): 479 (M+H).

Example 588

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone

Using 1-(4-hydroxyphenyl) ethanone, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.53-2.61 (10H, m), 3.51-3.93 (2H, m), 5.14-5.47 (1H, m), 6.95-7.74 (4H, m), 7.88-8.02 (2H, m), 8.53-8.68 (2H, m), 9.54-9.66 (1H, m), 10.60-10.88, 11.43-11.54 (total 1H, each m)

ESI-MS(m/e): 442 (M+H).

Example 589

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(difluoromethoxy) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(difluoromethoxy) pyridine-3-ol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

¹H-NMR(CD₃OD) δ : 1.92 and 2.18 (total 3H, each s), 1.98-2.57 (4H, m), 3.65-4.00 (2H, m), 5.41-5.48(1H, m), 7.03 and 7.07 (total 1H, each d, J = 8.8 Hz), 7.00-7.72 (5H, m), 7.94-8.00 (1H, m), 8.08 (1H, s), 8.25 (1H, t, J = 7.4 Hz), 8.73 (1H, s).

ESI-MS (m/e): 466 (M+H).

Example 590

6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-5-(4-pyrazin-2-yl phenoxy)-1H-benzimidazole

Using 4-pyrazin-2-yl phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CDCl₃) δ : 1.10-2.60 (7H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.70-7.80 (4H, m), 7.90-8.20 (2H, m), 8.50-8.80 (4H, m), 8.95-9.20 (1H, m), 9.50-9.75 (1H, m), 10.60-11.40 (1H, m).

ESI-MS (m/e): 478 (M+H).

Example 5914-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) benzonitrile

Using 4-cyanophenol, the title compound was obtained as a yellow oily substance by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.50-2.50 (7H, m), 3.50-3.90 (2H, m), 5.05-5.50 (1H, m), 6.65-7.80 (6H, m), 8.50-8.80 (2H, m), 9.50-9.70 (1H, m), 10.40-11.20 (1H, m).

ESI-MS (m/e): 425 (M+H).

Example 592Methyl 4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) benzoate

Using methyl 4-hydroxybenzoate, the title compound was obtained as a yellow oily substance by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.60-2.50 (7H, m), 3.50-4.00 (5H, m), 5.10-5.60 (1H, m), 6.70-7.80 (4H, m), 7.90-8.20 (2H, m), 8.50-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.60 (1H, m).

ESI-MS (m/e): 458 (M+H).

Example 5932-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide

Using 2'-fluorobiphenyl-4-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 182, a process based on this or a combination of these with a normal procedure.

¹H-NMR (DMSO-d₆) δ : 1.60-2.60 (4H, m), 3.20-4.20 (2H, m), 5.10-5.30 (1H, m), 5.60-5.90 (2H, m), 6.90-7.70 (11H, m), 7.90-8.10 (1H, m), 8.20-8.40 (1H, m), 8.60-8.80 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 5946-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure..

¹H-NMR (CDCl₃) δ : 1.60-2.80 (10H, m), 3.50-4.00 (2H, m), 5.15-5.60 (1H, m), 6.70-7.80 (5H, m), 7.90-8.20 (2H, m), 8.50-8.70 (1H, m), 9.50-9.70 (1H, m), 10.60-11.50 (1H, m).

ESI-MS (m/e): 482 (M+H).

Example 595

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Step 1Synthesis of 2-fluoro-N-methoxy-N-methylbenzamide

To 2-fluoro-4-nitrobenzoic acid 10 g suspended in pyridine 80 ml were added N-methoxy-N-methylamine hydrochloride 5.79 g and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 12.4 g, and the reaction liquor was stirred overnight at room temperature. Pyridine was eliminated by distillation under reduced pressure, and thereafter, water was added. The obtained precipitate was recovered by filtration and, by washing with water and drying, the title compound was obtained as a straw-coloured solid.

Step 2Synthesis of 4-amino-2-fluoro-N-methoxy-N-methylbenzamide

To 2-fluoro-N-methoxy-N-methylbenzamide 10.84 g suspended in methanol 60 ml and water 30 ml, ammonium chloride 15.2 g and iron powder 8 g were added, and the reaction liquor was heated under reflux for three hours. The reaction liquor was filtered using celite, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained residue was diluted with ethyl acetate and was washed using water and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/2) and the title compound was obtained as brown oily substance.

Step 3Synthesis of N-(3-fluoro-4-((N-methoxy-N-methylamino) carbonyl) phenyl) pyrazine-2-carboxamide

To 4-amino-2-fluoro-N-methoxy-N-methylbenzamide 3.7 g dissolved in pyridine 20 ml were added pyrazine-2-carboxylic acid 2.56 g and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 4.66 g, and the reaction liquor was stirred at room temperature for one hour. Pyridine was eliminated by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed using water and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and, by washing the obtained solid with mixed solvent of ethyl acetate and hexane, the title compound was obtained as a straw-coloured solid.

Step 4

Synthesis of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentinoyl)-3-fluorophenyl)
pyrazine-2-carboxamide

To (3R)-3-(tert-butyl (dimethyl) silyl) oxy-1-butyne 4.92 g dissolved in tetrahydrofuran 80 ml was added n-butyllithium (2.46M hexane solution) 10.8 ml at -78°C, and the reaction liquor was stirred at the same temperature for one hour. N-(3-fluoro-4-((N-methoxy-N-methylamino) carbonyl) phenyl) pyrazine-2-carboxamide 2.7 g dissolved in tetrahydrofuran 60 ml was added at -78°C, and the reaction liquor was warmed to room temperature, and thereafter, it was stirred for two hours. Water was added to the reaction liquid and the liquid extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/1), and the title compound was obtained as a yellow solid

Step 5

Synthesis of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentinoyl)-3-fluorophenyl)
pyrazine-2-carboxamide

To solution of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentinoyl)-3-fluorophenyl) pyrazine-2-carboxamide in mixture of 513 mg ethanol 20 ml and tetrahydrofuran 5 ml was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred under a hydrogen atmosphere for one hour 30 minutes. After eliminating the catalyst by filtration, the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/1), and the title compound was obtained as a straw-coloured solid.

Step 6

Synthesis of N-(4-((4R)-1,4-dihydroxy pentyl)-3-fluorophenyl) pyrazine-2-carboxamide

To a solution of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentinoyl)-3-fluorophenyl) pyrazine-2-carboxamide 340 mg in mixture of tetrahydrofuran 5 ml and methanol 10 ml was added sodium borohydride 89 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was concentrated down by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed with saturated ammonium chloride aqueous solution, and thereafter was dried with anhydrous magnesium sulphate. By eliminating under reduced pressure the solvent, crude product was obtained. To tetrahydrofuran 6 ml solution of the obtained crude product, tetrabutyl ammonium fluoride (1M tetrahydrofuran solution) 1.18 ml was added under ice cooling, and the reaction liquor was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate) and the title compound was obtained as a straw-coloured solid.

Step 7**Synthesis of N-(4-((5S)-1-acetyl-5-methylpyrrolidin-2-yl)-3-fluorophenyl)
pyrazine-2-carboxamide**

To N-(4-((4R)-1,4-dihydroxy pentyl)-3-fluorophenyl) pyrazine-2-carboxamide 147 mg suspended in chloroform 6 ml were added triethylamine 0.26 ml and methanesulphonyl chloride 0.11 ml, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was diluted with chloroform, washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. By eliminating the solvent by distillation under reduced pressure, crude product was obtained. To dimethylformamide 4 ml solution of the obtained crude product, sodium azide 30 mg was added under ice cooling, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, washed using water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. By eliminating the solvent under reduced pressure, crude product was obtained. To methanol 5 ml solution of the obtained crude product, copper sulfate pentahydrate 15 mg and sodium borohydride 52 mg were added, and the reaction liquor was stirred at room temperature for two hours. Sodium borohydride 35 mg was added, and the reaction liquor was stirred for 30 minutes. Further sodium borohydride 35 mg was added, and the reaction liquor was stirred for 30 minutes. The solvent was eliminated by distillation under reduced pressure and thereafter the residue was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. By eliminating the solvent by distillation under reduced pressure, crude product was obtained. Acetic anhydride 0.043 ml was added to chloroform 4 ml solution of the obtained crude product, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as straw-coloured oily substance.

Step 8**Synthesis of N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)
pyrazine-2-carboxamide**

To N-(4-((5S)-1-acetyl-5-methylpyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide 59 mg, fuming nitric acid 1 ml was added at room temperature, and the reaction liquor was stirred at the same temperature for 30 minutes. The reaction liquor was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art5744 (Merck Co.), ethyl acetate), and obtained the title compound as straw-coloured oily substance. (R_f : trans body > cis body)

Step 9**Production of****6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole**

To N-methylpyrrolidinone 1 ml solution of

N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide 10.4 mg were added 4-methansulphonyl-phenyl 9.2 mg, cesium carbonate 26.2 mg, and the reaction liquor was stirred at 90°C for one hour. Tin chloride (II) dihydrate 60 mg was added, and the reaction liquor was stirred at 90°C for one hour and at 100°C for two hours. To the reaction liquor were added ethyl acetate and saturated aqueous sodium bicarbonate, and precipitate was eliminated by filtration, thereafter extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel™ 60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as straw-coloured oily substance.

¹H-NMR (CDCl₃) δ : 1.31 and 1.33 (total 3H, each d, J = 6.0 Hz), 1.55-2.60 (7H, m), 3.03-3.10 (3H, m), 4.25-4.62 (1H, m), 5.20-5.44 (1H, m), 7.01-7.68 (4H, m), 7.85-7.97 (2H, m), 8.57-8.69 (2H, m), 9.56-9.63 (1H, m).

ESI-MS (m/e): 492 (M+H).

Example 596**N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl)-1H-benzimidazol-6-yl)pyrrolidin-1-yl)-2-oxoethanamine**

Using 2-methyl-2H-tetrazol-5-yl phenol, the title compound was obtained as a yellow oily substance by the same process as in Example 498 (Step 5)-(Step 8), a process based on these or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.80-2.50 (7H, m), 2.90-4.00 (4H, m), 4.30-4.50 (3H, m), 5.10-5.65 (1H, m), 7.10 (2H, m), 7.20-7.85 (3H, m), 7.80-7.95 (1H, m), 8.05-8.20 (2H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 510 (M+H).

Example 597**6-(1-acetyl pyrrolidin-2-yl)-5-((4'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 4'-fluorophenyl-4-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.66-2.43 (7H, m), 3.44-3.92 (2H, m), 5.21-5.60 (1H, m), 6.80-7.67 (11H, m), 7.77-7.91 (1H, m), 8.30-8.43 (1H, m), 8.53-8.67 (1H, m), 10.89-11.43 (1H, m).

ESI-MS (m/e): 493 (M+H).

Example 598

6-(1-acetyl pyrrolidin-2-yl)-5-((3'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 3'-fluorophenyl-4-ol, the title compound was obtained as a straw-coloured solid.

¹H-NMR (CDCl₃) δ : 1.67-2.44 (7H, m), 3.44-3.92 (2H, m), 5.22-5.58 (1H, m), 6.92-7.68 (11H, m), 7.78-7.93 (1H, m), 8.33-8.45 (1H, m), 8.56-8.68 (1H, m), 10.88-11.38 (1H, m).

ESI-MS (m/e): 493 (M+H).

Example 599

2-(5-((6-cyanopyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide

Using 6-cyanopyridin-3-ol, the title compound was obtained as a white solid the same process as in Example 162 and Example 182, a process based on these or a combination of these with a normal procedure.

¹H-NMR(CD80D) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 3.40-3.60 (1H, m), 3.70-3.80 (1H, m), 4.80-5.30 (1H, m), 6.60-6.75 (2H, m), 7.20-7.70 (3H, m), 7.80-8.20 (3H, m), 8.20-8.30 (1H, m), 8.50-8.65 (1H, m), 8.70-8.80 (1H, m).

ESI-MS (m/e): 426 (M+H).

Example 600

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide obtained in Example 595 (Step 8) and

4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenol, the title compound was obtained as pale yellow solid the same process as in Example 595 (Step 9), a process based on this or a combination of these with a normal procedure.

¹H-NMR (CDCl₃) δ : 1.33 and 1.34 (total 3H, each d, J = 6.0 Hz), 1.55-2.60 (7H, m), 2.68 and 2.70 (total 3H, each s), 4.26-4.62 (1H, m), 5.28-5.49 (1H, m), 7.03-8.12 (4H, m), 8.40-8.69 (3H, m), 9.57-9.63 (1H, 1).

ESI-MS (m/e): 497 (M+H).

Example 601

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyrazine-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)-phenoxy)-1H-benzi

midazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol and 5-methylpyrazine-2-carboxylic acid, the title compound was obtained as pale yellow solid the same process as in Example 306, a process based on this or a combination of these with a normal procedure.

¹H-NMR(CD₃OD) δ : 1.88-2.48 (7H, m), 2.63 and 2.64 (total 3H, each s), 3.61-3.99 (2H, m), 4.41 and 4.42 (total 3H, each s), 5.37-5.4 (1H, m), 7.15-7.55 (2H, m), 7.17 (2H, d, J = 8.8 Hz), 8.08 and 8.11 (total 2H, each d, J = 8.8 Hz), 8.64 (1H, s), 9.27 and 9.29 (total 1H, each s).
ESI-MS (m/e): 496 (M+H).

Example 6026-(1-acetyl-4-methylpyrrolidin-2-yl)-5-(4-(methanesulphonyl)
phenoxy)-2-pyridin-2-yl-1H-benzimidazole**Step 1**Synthesis of N-(3-fluoro-4-(3-methyl-3-butenoyl) phenyl) pyridine-2-carboxamide

Using pyridine-2-carboxylic acid, (2-methyl-2-propen-1-yl) magnesium chloride (0.50M tetrahydrofuran solution) 9.89 ml was added under ice cooling to tetrahydrofuran 10 ml solution of N-(3-fluoro-4-((methoxy (methyl) amino) carbonyl) phenyl) pyridine-2-carboxamide 500 mg obtained in accordance with the same process as in Example 145 (Step 3), a process based on this or a combination of these with a conventional procedure. The reaction liquor was stirred under ice cooling for three hours, and thereafter the reaction liquor was discharged into water, and extraction was carried out with ethyl acetate and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained.

Step 2Synthesis of N-(3-fluoro-4-(1-hydroxy-3-methyl-3-buten-1-yl) phenyl) pyridine-2-carboxamide

To N-(3-fluoro-4-(3-methyl-3-butenoyl) phenyl) pyridine-2-carboxamide 280 mg dissolved in methanol 5 ml solution, sodium borohydride 88.8 mg was added. The reaction liquor was stirred at room temperature for three hours, and thereafter, it was discharged into saturated ammonium chloride aqueous solution, and extraction was carried out with ethyl acetate and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1) and the title compound was obtained.

Step 3Synthesis of N-(4-(1,4-dihydroxy-3-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide

Borane-methyl sulphide complex (1M dichloromethane solution) 1.20 ml was added under ice cooling to cyclohexene 0.082 ml dissolved in tetrahydrofuran 5 ml solution. The reaction liquor was stirred under ice cooling for ten minutes, and thereafter, N-(3-fluoro-4-(1-hydroxy-3-methyl-3-buten-1-yl) phenyl) pyridine-2-carboxamide 301 mg dissolved in tetrahydrofuran 3 ml solution was added, and the reaction liquor was stirred at room temperature for one hour. 5N sodium hydroxide aqueous solution and 35 % hydrogen peroxide aqueous solution 0.50 ml were added successively to the reaction liquor and stirred at room temperature for ten minutes. The reaction liquor was discharged into saturated ammonium chloride aqueous solution and was extracted with acetic acid ethyl ester, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 9/1) and the title compound was obtained.

Step 4

Synthesis of N-(3-fluoro-4-(4-methylpyrrolidin-2-yl) phenyl) pyridine-2-carboxamide

To N-(4-(1,4-dihydroxy-3-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide 236 mg dissolved in chloroform 5 ml solution, were added under ice cooling successively triethylamine 0.62 ml and methane sulphonyl chloride 0.213 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was discharged into saturated aqueous sodium bicarbonate and was extracted with chloroform, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To dimethylformamide 3 ml solution of the obtained crude product, sodium azide 53.0 mg was added under ice cooling. The reaction liquor was stirred under ice cooling for 30 minutes and thereafter, stirred at room temperature for three hours. The reaction liquor was diluted with ethyl acetate and was washed using water, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To methanol 4 ml solution of the obtained crude product, copper sulfate pentahydrate 20 mg and sodium borohydride 168 mg were successively added. The reaction liquor was stirred at room temperature for four hours, and thereafter, it was discharged into saturated aqueous sodium bicarbonate, and it was extracted with chloroform, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To chloroform 3 ml solution of the obtained crude product, acetic anhydride 0.050 ml was added, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/3), and the title compound was thereby obtained.

Step 5

Synthesis of N-(4-(1-acetyl-4-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)
pyridine-2-carboxamide

N-(3-fluoro-4-(4-methylpyrrolidin-2-yl) phenyl) pyridine-2-carboxamide 70.7 mg was dissolved in fuming nitric acid 1 ml, and the reaction liquor was stirred at room temperature for ten minutes. The reaction liquor was discharged into saturated aqueous sodium bicarbonate and was extracted with acetic acid ethyl ester, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2), and the title compound was obtained.

Step 6

Production of 6-(1-acetyl-4-methylpyrrolidin-2-yl)-5-(4-(methanesulphonyl)
phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To 2 ml N-methyl-pyrrolidinone solution of

N-(4-(1-acetyl-4-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide 15 mg were added successively 4-(methanesulphonyl) phenol 13.4 mg and cesium carbonate 44.9 mg, and the reaction liquor was stirred at 90°C for one hour. After the addition of tin chloride dihydrate 43.8 mg to the reaction liquor, it was warmed to 100°C and was stirred for two hours. The reaction liquor was dissolved in ethyl acetate, and thereafter, it was washed with saturated aqueous sodium bicarbonate, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F₂₅₄, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

¹H-NMR (CDCl₃) δ : 0.80-2.63 (9H, m), 3.00-4.40 (2H, m), 3.05 and 3.08 (total 3H, each s), 5.03-5.43 (1H, m), 7.00-7.73 (5H, m), 7.83-7.98 (3H, m), 8.33-8.43 (1H, m), 8.62-8.70 (1H, m), 10.62-10.80 (1H, m).

ESI-MS (m/e): 491 (M+H).

Example 603

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl)
oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide obtained in Example 595 (Step 8) and 6-(methoxymethyl) pyridin-3-ol, the title compound was obtained as pale yellow oily substance in accordance with Example 595 (Step 9), a process based on this or a combination of these with a conventional procedure.

¹H-NMR (CDCl₃) δ : 1.10-2.22 (10H, m), 3.48 and 3.50 (total 3H, each s), 4.26-4.62 (1H, m), 4.57 and 4.59 (total 2H, each s), 5.33-5.52 (1H, m), 7.20-7.50 (4H, m), 8.40-8.70 (3H, m), 9.57-9.63 (1H, m).

ESI-MS (m/e): 459 (M+H).

Reference Example 1

[1,2,4] thiadiazole-5-carboxylic acid

To thio oxamic acid ethyl ester 1 g dissolved in chloroform 10 ml was added N,N-dimethylformamide dimethylacetal 2 ml, and the reaction liquor was stirred at room temperature for four hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/2) and amidine body 1.1 g was obtained as red oily substance.

To amidine body 1.09 g and pyridine 0.95 ml dissolved in ethanol 18 ml was added hydroxylamine-O-sulfonic acid 721 mg dissolved in ethanol 20 ml, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed with saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1) and [1,2,4] thiadiazole-5-carboxylic acid ethyl ester was obtained as straw-coloured oily substance. To the obtained [1,2,4] thiadiazole-5-carboxylic acid ethyl ester 300 mg dissolved in methanol 8 ml solution, 1N sodium hydroxide aqueous solution 5.7 ml was added, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the residue was neutralized using 2 N hydrochloric acid. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the residue was washed with chloroform-methanol = 10/1, and the title compound was obtained as a white solid by eliminating the obtained organic layer under reduced pressure.

Reference Example 2

2-difluoromethoxy-pyridin-3-ol

To 3-benzyloxy-2-hydroxypyridine 2 g suspended in acetonitrile 40 ml were added sodium carbonate 2.1 g and difluoro fluorosulfonyl acetic acid 1.24 ml, and the reaction liquor was stirred at room temperature for one hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-4/1) and difluoromethoxy body was obtained as straw-coloured oily substance. To difluoromethoxy body 2.38 g dissolved in methanol 25 ml solution, 10 % palladium-carbon catalyst 500 mg was added, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for one hour. The catalyst

was eliminated by filtration by celite, and, by eliminating the solvent under reduced pressure, the title compound was obtained as light purple oily substance.

Reference Example 3

6-methanesulphonyl-pyridin-3-ol

In 3-bromo-6-methanesulphonyl-pyridine 4.72 g dissolved in dimethylsulfoxide 8 ml were added bis (pinacolate) diboron 6.6 g, potassium acetate 5.9 g and (1,1'-bis (diphenylphosphino) ferrocene) dichloroparadium (II) dichloromethan complex 980 mg, and the reaction liquor was stirred at 80°C for two hours. Acetic acid ethyl ester and water were added to the reaction liquor, insolubles substance were eliminated by filtration with celite and thereafter, the organic layer was separated. The organic layer was washed using water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. 5N sodium hydroxide aqueous solution 60 ml and 30 % hydrogen peroxide water 30 ml were added to tetrahydrofuran 200 ml solution of the obtained residue at 0°C, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with diethyl ether and thereafter washed using water. The aqueous layer was acidified with 5 N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. By washing the obtained residue with mixed solvent of chloroform and hexane, the title compound was obtained as a brown solid.

Reference Example 4

6-ethanesulfonyl-pyridin-3-ol

Using 3-chloro-6-ethane sulfonyl-pyridine, the title compound was obtained the same method as in Reference Example 3, process base on this or by combining these with the normal method.

Reference Example 5

(2R,4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide

Step 1

Synthesis of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester

To (2R,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 3.61 g dissolved in dimethylformamide 60 ml were added successively tert-butyl diphenyl silyl chloride 2.32 g and imidazole 2.32 g, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure,

and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2) and the title compound was obtained.

Step 2

Synthesis of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

To (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2.62 g dissolved in pyridine 30 ml solution obtained in (Step 1) were added successively 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 1.50 g and O,N-dimethyl hydroxylamine hydrochloride 761 mg, and the reaction liquor was stirred overnight at room temperature. The solvent of the reaction liquor was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained.

Step 3

Synthesis of (2R,4R)-4-hydroxy-2-methoxy-methyl-carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester

To tetrahydrofuran 30 ml solution of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester 2.04 g obtained in (Step 2) was added tetrabutyl ammonium fluoride (1M tetrahydrofuran solution) 7.46 ml, and the reaction liquor was stirred at room temperature for 20 minutes. The solvent of the reaction liquor was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/3) and the title compound was obtained.

Step 4

Production of (2R,4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide

To ethanol 20 ml solution of (2R,4R)-4-hydroxy-2-methoxy-methyl-carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester 600 mg obtained in (Step 3) was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred overnight under a hydrogen atmosphere. The reaction liquor was stirred under hydrogen atmosphere over night. The catalyst was eliminated by filtration with celite, thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

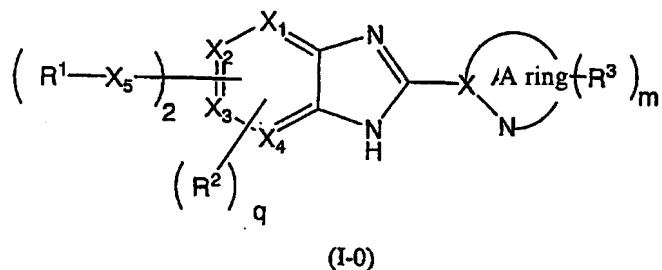
Possible Commercial Applications

The substituted benzimidazole derivatives in accordance with this invention and represented by aforesaid formula (I-O) demonstrate excellent glucokinase activity and therefore are useful in the

field of medicine, treatment and prevention of diabetes, diabetes complications and obesity.

Patent Claims

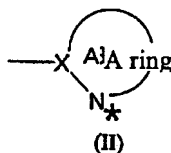
1. A compound represented by Formula (I-0), or pharmacologically acceptable salts thereof



[wherein, X denotes a carbon atom or nitrogen atom,

X₁, X₂, X₃ and X₄ each independently denote carbon atom or nitrogen atom,

A ring denotes a 5-6 membered nitrogen containing heteroaromatic ring represented by formula (II)



which may contain 1-3 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (excluding the nitrogen atom represented by N* in formula II), or a bicyclic ring in which the said nitrogen containing heteroaromatic ring and phenyl or pyridyl are condensed,

R¹ denotes aryl or a 4-10 membered monocyclic or bicyclic heterorings containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said R¹ may be each independently substituted with 1 to 3 R⁴, moreover, when the said heteroring is an aliphatic heteroring, it may contain 1 or 2 double bonds),

R² each independently denote hydroxy, formyl, -CH_{3-a}F_a, -OCH_{3-a}F_a, amino, CN, halogen, C₁₋₆ alkyl or (CH₂)₁₋₄OH,

R³ denotes -C₁₋₆ alkyl, -(CH₂)₁₋₆-OH, -C(O)-OC₁₋₆ alkyl, -(CH₂)₁₋₆-OC₁₋₆ alkyl, -(CH₂)₁₋₆-NH₂, cyano, -C(O)-C₁₋₆ alkyl, halogen, -C₂₋₆alkenyl, -OC₁₋₆alkyl, -COOH, -OH or oxo,

R⁴ each independently,

-C₁₋₆ alkyl (the said alkyl may be substituted with the same or different 1 to 3 hydroxy, halogen,

-OC(O)-C₁₋₆ alkyl (the said alkyl may be substituted with 1 to 3 halogen), or -OC₁₋₆ alkyl)

-C₃₋₇ cycloalkyl,

-C₂₋₆ alkenyl,

-C(O)-N(R⁵¹)R⁵²,

-S(O)₂-N(R⁵¹)R⁵²,

-O-C₁₋₆ alkyl (the said C₁₋₆ alkyl may be substituted with halogen or N(R⁵¹)R⁵²),

-S(O)₀₋₂-C₁₋₆ alkyl,

-C(O)-C₁₋₆ alkyl (the said C₁₋₆ alkyl may be substituted with halogen, amino, CN, hydroxy, -O-

C₁₋₆ alkyl, -CH_{3-a}F_a, -OC(O)-C₁₋₆ alkyl, -N (C₁₋₆ alkyl)C(O)O-C₁₋₆ alkyl, -NH-C(O)O-C₁₋₆ alkyl, phenyl, -N(R⁵¹)R⁵²-NH-C(O)-C₁₋₆ alkyl, -N (C₁₋₆ alkyl)-C(O)-C₁₋₆ alkyl or -NH-S(O)₀₋₂-C₁₋₆ alkyl),

-C(S)-C₃₋₇ cycloalkyl,

-C(S)-C₁₋₆ alkyl,

-C(O)-O-C₁₋₆ alkyl,

-(CH₂)₀₋₄-N(R⁵³)-C(O)-R⁵⁴,

-N(R⁵³)-C(O)-O-R⁵⁴,

-C(O)-aryl (the said aryl may be substituted with halogen),

-C(O)-heteroaromatic ring,

-C(O)-aliphatic hetero ring,

hetero ring (the said hetero ring may be substituted with -C₁₋₆ alkyl (the said -C₁₋₆ alkyl may be substituted with halogen or -O-C₁₋₆ alkyl),

phenyl (the said phenyl may be substituted with halogen, -C₁₋₆ alkyl, -O-C₁₋₆ alkyl),

halogen, CN, formyl, COOH, amino, oxo, hydroxy, hydroxy amidino or nitro,

R⁵¹ and R⁵² each independently denote hydrogen atom, -C₁₋₆ alkyl,

or 4-7 membered hetero ring formed by linking nitrogen atom, R⁵¹ and R⁵² together,

R⁵³ denotes a hydrogen atom or -C₁₋₆ alkyl,

R⁵⁴ denotes -C₁₋₆ alkyl or,

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R⁵³ and R⁵⁴, and -N-C(O)- together or

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R⁵³ and R⁵⁴, and -N-C(O)-O- together (the said aliphatic hetero ring may be substituted with oxo, and moreover, the said aliphatic hetero ring may contain 1 or 2 double bonds in the ring),

X₅ denotes -O-, -S-, -S(O)-, -S(O)₂-, single bond or -O-C₁₋₆-alkyl",

a denotes, each independently, an integer of 1, 2 or 3,

q denotes an integer of 0-2,

m denotes an integer of 0-2]

(wherein the following cases were excluded:

the case wherein one of X₅ is -O-, -S-, -S(O)- or -S(O)₂-, and the other X₅ is single bond, and also R¹ is aryl or nitrogen-containing aromatic heteroring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said aryl may be substituted with 1-3 R⁴),

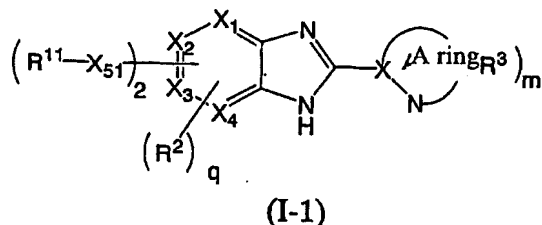
the case wherein both X⁵ are single bonds, or

the case wherein both R¹ are aliphatic heteroring).

2. A compound in accordance with Claim 1 or pharmacologically acceptable salts thereof, wherein X₁ to X₄ are all carbon atoms.

3. A compound in accordance with Claim 1 or pharmacologically acceptable salts thereof, wherein X_5 is -O-, -S-, -S(O)-, -S(O)₂- or single bond.

4. A compound in accordance with Claim 1 represented by formula (I-1) or pharmacologically acceptable salts thereof



[in the formula, R^{11} denotes phenyl which may be substituted with 1-3 R^4 or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4), and also

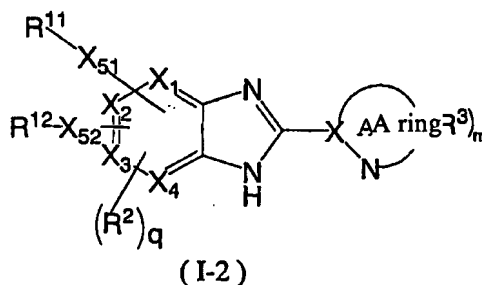
X_{51} denotes -O-, -S-, -S(O)- or -S(O)₂-, and the other symbols are the same as above].

5. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein both R^{11} are phenyl which may be substituted with 1-3 R^4 .

6. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein both R^{11} are 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4).

7. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein one of the R^{11} is phenyl which may be substituted with 1-3 R^4 and also the other R^{11} is 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4).

8. A compound in accordance with Claim 1 represented by formula (I-2) or pharmacologically acceptable salts thereof



[in the formula, R^{11} denotes phenyl which may be substituted with 1-3 R^4 or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4),

R^{12} denotes 4 to 7-membered nitrogen-containing heteroring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said R^{12} may be substituted with 1-3 R^4 , and moreover, when the said hetero ring is an aliphatic hetero ring, it may contain 1 or 2 double bonds),

X_{51} is -O-, -S-, -S(O)- or -S(O)₂-,

X_{52} is -O-, -S-, -S(O)-, -S(O)₂- or single bond, and the other symbols are the same as above].

9. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein R^{12} is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3 R^4 . And also X_{52} is a single bond, or

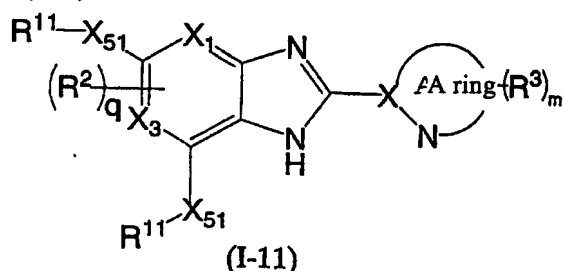
R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4 . And also X_{52} is -O-, -S-, -S(O)- or -S(O)₂-.

10. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein R^{12} is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3 R^4 . And also X_{52} is a single bond.

11. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4 . And also X_{52} is -O-, -S-, -S(O)- or -S(O)₂-.

12. A compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2), R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4 . And also X_{52} is -O-.

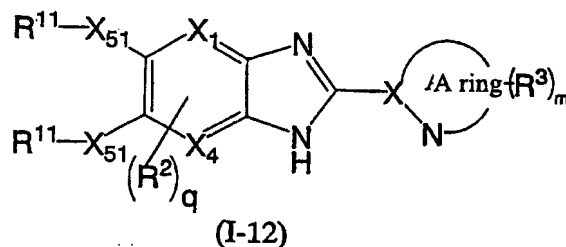
13. A compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-11)



(each symbol is the same as above).

14. A compound in accordance with Claim 13 or pharmacologically acceptable salts thereof, wherein both X_{51} are -O-.

15. A compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-12)



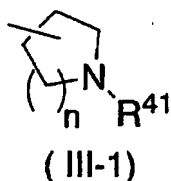
(each symbol is the same as above).

16. A compound in accordance with Claim 15 or pharmacologically acceptable salts thereof,
©Rising Sun Communications Ltd.

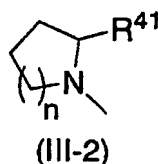
<http://www.risingsun.co.uk>

wherein both X_{51} are -O-.

17. A compound in accordance with Claim 10 or pharmacologically acceptable salts thereof, wherein R^{12} is formula (III-1)



or formula (III-2)



[wherein, n denotes an integer of 1-3, and R^{41} denotes the group same as the aforesaid R^4].

18. A compound in accordance with any one of Claims 1 to 17 or pharmacologically acceptable salts thereof, wherein the A ring is thiazolyl, imidazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, pyrazolyl or pyrimidinyl wll of which may be substituted with 1-3 of aforesaid R^4 .

19. A compound or pharmacologically acceptable salts thereof, wherein the compound represented by formula (I-0) is

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole,
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimida
zole,
5-(2-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimida
zole,
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-
1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-
1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(1-methyl-1H-
pyrazol-3-yl)-1H-benzimidazole,
5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazo

le,
5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole
,
5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole
,
5-(2,6-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole
,
5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
le,
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
le,
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
le,
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
le,
5-(2-cyanopyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
e,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
e,
5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

ole,

5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2-fluoro-phenoxy)-2-(pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

,

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole,

4-(2-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,3-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

,

4-(2,5-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

,

4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

1-(2-(6-(5-bromo-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-et

hanone,
 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carbox
 amide,
 2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrro
 lidin-1-yl)-ethanone,
 1-(2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl
)-ethanone,
 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-et
 hanone,
 2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidi
 n-1-yl)-ethanone,
 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile,
 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-
 methylamino-ethanone,
 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-
 yl)-ethanone,
 1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidi
 n-1-yl)-ethanone,
 N-(5-(6-[1-acetyl-pyrrolidin-2-yl]-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-aceta
 mide,
 1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrroli
 din-1-yl)-ethanone,
 N-(2-(2-[6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl]-pyrrolidin-1-yl
)-2-oxo-ethyl)-acetamide,
 6-(1-acetylpyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole •
 mono trifluoroacetate,
 1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)
 pyridine-2(1H)-one,
 6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)
 oxy)-2-pyridin-2-yl-1H-benzimidazole,
 (2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)
 pyrrolidin-1-yl)-2-oxoethyl) methylamine,
 6-(1-acetylpyrrolidin-2-yl)-5-((6-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)
 oxy)-2-pyridin-2-yl-1H-benzimidazole,
 6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)
 phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
 5-(1-acetyl-3-fluoropyrrolidin-2-yl)-6-(4-(methanesulphonyl)
 phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-(6-(methoxymethylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol,
2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide,
5'-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one,
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,
6-(1-acetylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
6-(1-acetyl-3-fluoropyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,
6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-1H-benzimidazole,
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,
1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone,
6-(1-acetylpyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,
N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanamine,
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone,

1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone,

1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone, or

1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrrolidin-2-yl)-ethanone.

20. A medicinal composition comprising the following (1)-(3) to be used for therapy, prevention and/or delay of onset of type II diabetes mellitus;

(1) a compound in accordance with any one of Claims 1-19,

(2) a compound of 1 or 2 or more, selected from the group comprising following (a)-(h),

(a) other glucokinase activator,

(b) bis-guanide,

(c) PPAR agonist,

(d) insulin,

(e) somatostatin,

(f) α -glucosidase inhibitor,

(g) insulin, and

(h) DPF-IV (dipeptidyl peptidase IV) inhibitor

(3) a pharmacologically acceptable carrier.

21. A glucokinase activator containing as effective ingredient a compound in accordance with any one of Claims 1-19 or pharmacologically acceptable salts thereof.

22. A therapeutic and/or preventive agent of diabetes mellitus containing as effective ingredient a compound in accordance with any one of Claims 1-20 or pharmacologically acceptable salts thereof.

23. A therapeutic and/or preventive agent of obesity containing as effective ingredient a compound in accordance with any one of Claims 1-20 or pharmacologically acceptable salts thereof.

Rising Sun Communications Ltd. Terms and Conditions (Abbreviated)

Rising Sun Communications Ltd. shall not in any circumstances be liable or responsible for the accuracy or completeness of any translation unless such an undertaking has been given and authorised by Rising Sun Communications Ltd. in writing beforehand. More particularly, Rising Sun Communications Ltd. shall not in any circumstances be liable for any direct, indirect, consequential or financial loss or loss of profit resulting directly or indirectly from the use of any translation or consultation services by the customer.

Rising Sun Communications Ltd. retains the copyright to all of its' translation products unless expressly agreed in writing to the contrary. The original buyer is permitted to reproduce copies of a translation for their own corporate use at the site of purchase, however publication in written or electronic format for resale or other dissemination to a wider audience is strictly forbidden unless by prior written agreement.

The Full Terms and Conditions of Business of Rising Sun Communications may be found at the web site address <http://www.risingsun.co.uk/Terms_of_business.html>

(19) 世界知的所有権機関
国際事務局(43) 国際公開日
2005 年 7 月 14 日 (14.07.2005)

PCT

(10) 国際公開番号
WO 2005/063738 A1(51) 国際特許分類⁷: C07D 401/04,
401/12, 401/14, 413/04, 413/14, 417/04, A61K 31/4192,
31/4196, 31/4245, 31/426, 31/427, 31/433, 31/4439,
31/444, 31/4709, 31/496, 31/497, 31/506, 31/5377, A61P
3/04, 3/10, 13/12, 25/00, 43/00

(21) 国際出願番号: PCT/JP2004/019843

(22) 国際出願日: 2004 年 12 月 28 日 (28.12.2004)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願 2003-436992
2003 年 12 月 29 日 (29.12.2003) JP
特願 2004-235696 2004 年 8 月 13 日 (13.08.2004) JP(71) 出願人 (米国を除く全ての指定国について): 萬有製
薬株式会社 (BANYU PHARMACEUTICAL CO.,LTD)
[JP/JP]; 〒1038416 東京都中央区日本橋本町 2 丁目
2 番 3 号 Tokyo (JP).

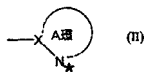
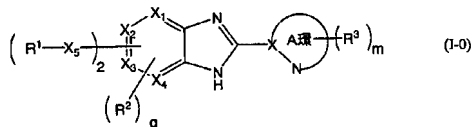
(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 野々下 克昌
(NONOSHITA, Katsumasa) [JP/JP]; 〒3002611 茨城県
つくば市大久保 3 番地 萬有製薬株式会社 つくば研究
所内 Ibaraki (JP). 荻野 悦夫 (OGINO, Yoshio) [JP/JP]; 〒3002611 茨城県つくば市大久保 3 番地 萬有製薬株式
会社 つくば研究所内 Ibaraki (JP). 石川 誠 (ISHIKAWA,
Makoto) [JP/JP]; 〒3002611 茨城県つくば市大久保
3 番地 萬有製薬株式会社 つくば研究所内 Ibaraki (JP).
坂井 富美子 (SAKAI, Fumiko) [JP/JP]; 〒3002611 茨城
県つくば市大久保 3 番地 萬有製薬株式会社 つくば
研究所内 Ibaraki (JP). 中嶋 弘 (NAKASHIMA, Hiroshi)
[JP/JP]; 〒3002611 茨城県つくば市大久保 3 番地 萬
有製薬株式会社 つくば研究所内 Ibaraki (JP). 長江 義
和 (NAGAE, Yoshikazu) [JP/JP]; 〒3002611 茨城県つ
くば市大久保 3 番地 萬有製薬株式会社 つくば研究
所内 Ibaraki (JP). 塚原 大介 (TSUKAHARA, Daisuke)
[JP/JP]; 〒3002611 茨城県つくば市大久保 3 番地 萬
有製薬株式会社 つくば研究所内 Ibaraki (JP). 荒川 佳
介 (ARAKAWA, Keisuke) [JP/JP]; 〒3002611 茨城県つ
くば市大久保 3 番地 萬有製薬株式会社 つくば研究
所内 Ibaraki (JP). 西村 輝之 (NISHIMURA, Teruyuki)
[JP/JP]; 〒3002611 茨城県つくば市大久保 3 番地 萬有
製薬株式会社 つくば研究所内 Ibaraki (JP). 永木 淳一
(EIKI, Jun-ichi) [JP/JP]; 〒3002611 茨城県つくば市大
久保 3 番地 萬有製薬株式会社 つくば研究所内 Ibaraki
(JP).(74) 共通の代表者: 萬有製薬株式会社 (BANYU PHAR-
MACEUTICAL CO.,LTD); 〒1038416 東京都中央区
日本橋本町 2 丁目 2 番 3 号 Tokyo (JP).(81) 指定国 (表示のない限り、全ての種類の国内保護が
可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM,

[続葉有]

(54) Title: NOVEL 2-HETEROARYL-SUBSTITUTED BENZIMIDAZOLE DERIVATIVE

(54) 発明の名称: 新規 2-ヘテロアリアル置換ベンズイミダゾール誘導体

(57) Abstract: A glucokinase activator; a therapeutic and/or preventive agent for diabetes or a therapeutic and/or preventive agent for complications of diabetes, such as retinopathy, nephropathy, neurosis, ischemic heart disease, and arteriosclerosis; and a therapeutic and/or preventive agent for obesity. The glucokinase activator is characterized by containing either a 2-heteroaryl-substituted benzimidazole derivative represented by the general formula (I-0): 1 RING A (I-0) [wherein X represents carbon or nitrogen; X₁, X₂, X₃, and X₄ each independently represents carbon or nitrogen; ring A represents, e.g., a 5- or 6-membered nitrogenous aromatic heterocycle represented by the formula (II): 1 RING A (II) (wherein X represents carbon or nitrogen); R¹ represents aryl, etc.; R² represents hydroxy, etc.; R³ represents -(C₁₋₆ alkyl), etc.; R⁴ represents -(C₁₋₆ alkyl), etc.; X₅ represents -O-, etc.; a is 1, 2, or 3; q is an integer of 0 to 2; and m is an integer of 0 to 2] or a pharmaceutically acceptable salt of the derivative.

[続葉有]



DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:

— 国際調査報告書

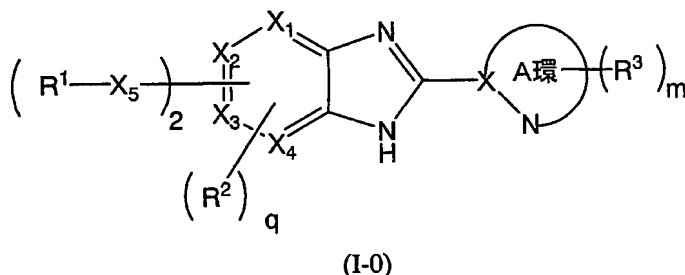
(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE,

2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

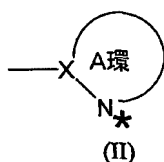
(57) 要約:

グルコキナーゼ活性化剤を提供し、糖尿病の治療及び／又は予防剤、或いは、網膜症、腎症、神経症、虚血性心疾患、動脈硬化等の糖尿病の治療及び／又は予防剤として、更には、肥満の治療及び／又は予防剤を提供するものである。

一般式 (I-0)



[式中、Xは、炭素原子又は窒素原子を示し、X₁、X₂、X₃及びX₄は、それぞれ独立して、炭素原子又は窒素原子を示し、A環は、式 (I I)



(式中、Xは炭素原子又は窒素原子を示す) で表される5乃至6員の含窒素芳香族複素環等を示し、R¹は、アリール等を示し、R²はヒドロキシ等を示し、R³は、-C₁₋₆アルキル等を示し、R⁴は-C₁₋₆アルキル等を示し、X₅は、-O-等を示し、aは、1、2又は3の整数を示し、qは、0乃至2の整数を示し、mは0乃至2の整数を示す] で表される2-ヘテロアリール置換ベンズイミダゾール誘導体又はその薬学的に許容される塩を含有することを特徴とするグルコキナーゼ活性化剤。

明 細 書

新規 2-ヘテロアリール置換ベンズイミダゾール誘導体

技術分野

本発明は、医薬の分野において有用な 2-ヘテロアリール置換ベンズイミダゾール誘導体を有効成分として含有するグルコキナーゼ活性化剤に関する。さらに、新規な新規 2-ヘテロアリール置換ベンズイミダゾール誘導体に関する。

背景技術

グルコキナーゼ (GK) (ATP : D-hexose 6-phospho transferase, EC 2. 7. 1. 1) は、哺乳類の 4 種のヘキソキナーゼのうちの一つ (ヘキソキナーゼ I V) である。ヘキソキナーゼは、解糖系の一番はじめの段階の酵素でグルコースからグルコース 6 磷酸への反応を触媒する。グルコキナーゼは、主に肝臓と膵臓ベータ細胞に発現が限局しており、それらの細胞のグルコース代謝の律速段階を制御することで、体全体の糖代謝に重要な役割を果たしている。肝臓と膵臓ベータ細胞のグルコキナーゼは、それぞれスプライシングの違いにより N 末 15 アミノ酸の配列が異なっているが、酵素学的性質は同一である。グルコキナーゼ以下の 3 つのヘキソキナーゼ (I, II, III) は、1 mM 以下のグルコース濃度で酵素活性が飽和してしまうのに対し、グルコキナーゼのグルコースに対する K_m は、8 mM と生理的な血糖値に近い。従って、正常血糖 (5 mM) から、食後血糖上昇 (10-15 mM) の血糖変化に呼応した形でグルコキナーゼを介した細胞内グルコース代謝の亢進が起こる。

10 年ほど前から、グルコキナーゼは膵臓ベータ細胞や肝臓のグルコースセンサーとして働くという仮説が提唱された [例えば、ガーフィンケル (Garfinkel D) ら著、コンピュータ モデリング アイデンティファイズ グルコキナーゼ アズ グルコース センサー オブ パンクレアティック ベータ セルズ (Computer modeling identifies glucokinase as glucose sensor of pancreatic beta-cells)、アメリカン ジャーナル

フィジオロジ (American Journal Physiology)、第247巻 (3 Pt 2)、1984年、p527-536参照]。

最近のグルコキナーゼ遺伝子操作マウスの結果から、実際にグルコキナーゼは全身のグルコース恒常性に重要な役割を担うことが明らかになっている。グルコキナーゼ遺伝子を破壊したマウスは生後まもなく死亡する [例えば、グルペ (Grupe A) ら著、トランスジェニック ノックアウト リピール ア クリティカル リクワイヤメント フォー パンクレアティク ベータセルズ グルコキナーゼ イン メインテイニング グルコース ホメオスタシス (Transgenic knockouts reveal a critical requirement for pancreatic beta cell glucokinase in maintaining glucose homeostasis)、セル (Cell)、第83巻、1995年、p69-78参照] が、一方グルコキナーゼを過剰発現させた正常及び糖尿病マウスは血糖値が低くなる [例えば、フェレ (Ferre T) ら著、コレクシオン ディアベティック アルターネイションズ バイ グルコキナーゼ (Correction of diabetic alterations by glucokinase)、プロシーディングズ オブ ザ ナショナル アカデミー オブ サイエンシズ オブ ザ ユーエス エー (Proceedings of the National Academy of Sciences of the U. S. A.)、第93巻、1996年、p7225-7230参照]。

グルコース濃度上昇によって、膵臓ベータ細胞と肝細胞の反応は、異なるがいずれも血糖を低下させる方向に対応する。膵臓ベータ細胞は、より多くのインスリンを分泌するようになるし、肝臓は糖を取り込みグリコーゲンとして貯蔵すると同時に糖放出も低下させる。

このようにグルコキナーゼ酵素活性の変動は、肝臓および膵臓ベータ細胞を介した哺乳類のグルコースホメオスタシスにおいて重要な役割を果たしている。MODY2 (maturity-onset diabetes of the young) と呼ばれる若年に糖尿病を発症する症例においてグルコ

キナーゼ遺伝子の突然変異が発見され、グルコキナーゼ活性の低下が血糖上昇の原因となっている [例えば、ビオンネット (Vionnet N) ら著、ノンセンス ミューテイション イン ザ グルコキナーゼ ジーン コー
5 ジーズ アーリー-オンセット ノン-インシュリン-ディペンデント
ディアベテス メリィタス (Nonsense mutation in the glucokinase gene causes early-on
set non-insulin-dependent diabetes mellitus)、ネイチャー ジェネティクス (Nature Gene
tics)、第356巻、1992年、p721-722参照]。

10 一方グルコキナーゼ活性を上昇させる突然変異をもつ家系も見つかっており、このような人たちは低血糖症状を示す [例えば、グレイサー (Glaser B) ら著、ファミリアル ハイパーインシュリニズム コーズド バイ
アン アクティベィティング グルコキナーゼ ミューテイション (Fami
15 lial hyperinsulinism caused by an activating glucokinase mutation)、ニュー
イングランド ジャーナル メディシン (New England Journal Medicine)、第338巻、1998年、p226-230参
照]。

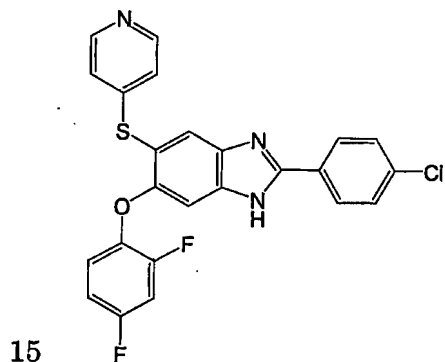
これらのことからグルコキナーゼはヒトでもグルコースセンサーとして働き、
20 グルコース恒常性に重要な役割を果たしている。一方多くのII型糖尿病患者
でグルコキナーゼセンサーシステムを利用した血糖調節は可能と考えられる。
グルコキナーゼ活性化物質には膵臓ベータ細胞のインスリン分泌促進作用と肝
臓の糖取り込み亢進および糖放出抑制作用が期待できるので、II型糖尿病患者
の治療薬として有用と考えられる。

25 近年、膵臓ベータ細胞型グルコキナーゼがラット脳の、中でも特に摂食中枢
(Ventromedial hypothalamus, VMH) に限局して発現していることが明らかにされた。VMHの約2割の神経細胞は、グル
コースレスポンスニューロンと呼ばれ、従来から体重コントロールに重要な
役割を果たすと考えられてきた。ラットの脳内へグルコースを投与すると摂食

量が低下するのに対して、グルコース類縁体のグルコサミン脳内投与によってグルコース代謝抑制すると過食となる。電気生理学的実験からグルコースレスポンシブニューロンは生理的なグルコース濃度変化（5－20 mM）に呼応して活性化されるがグルコサミン等でグルコース代謝抑制すると活性抑制が認められる。VHMのグルコース濃度感知システムには膵臓ベータ細胞のインスリン分泌と同様なグルコキナーゼを介したメカニズムが想定されている。従って肝臓、膵臓ベータ細胞に加えVHMのグルコキナーゼ活性化を行う物質には血糖是正効果のみならず、多くのⅡ型糖尿病患者で問題となっている肥満をも是正できる可能性がある。

- 10 上記の記載から、グルコキナーゼ活性化作用を有する化合物は、糖尿病の治療剤及び／又は予防剤として、或いは、網膜症、腎症、神経症、虚血性心疾患、動脈硬化等の糖尿病の慢性合併症の治療及び／又は予防剤として、更には肥満の治療及び／又は予防剤として有用である。

ベンズイミダゾール誘導体としては、例えば、下記式

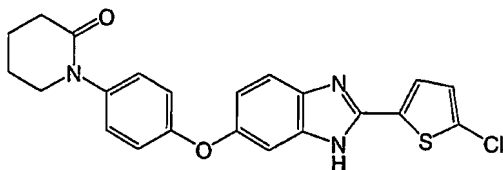


で表される化合物が記載されている〔例えば、特開2000-026430参照〕。

- 20 上記式で記載される化合物は、ベンズイミダゾール骨格の2位に置換基を有するものの、その置換基は、4-クロロフェニルであり、本発明に係るA環とは異なるものである。

さらに、当該化合物の用途は、インターロイキン産生抑制剤に関するものであり、当該化合物が、糖尿病の治療及び／又は予防に有用であるとの記載はなく、また、これを示唆する記載もない。

また、ベンズイミダゾール誘導体としては、例えば、下記式



で表される化合物が記載されている（例えば、WO 2004 017963 参照）。

- 5 上記式で記載されている化合物は、ベンズイミダゾール骨格のベンゼン環上に置換基を1つしか有しておらず、また、ベンズイミダゾール骨格の2位に置換基を有しているものの、その置換基は5-クロロチエニルであり、本発明に係るA環とは異なるものである。

- また、当該化合物の用途は、Factor Xa及びFactor VIIa阻害剤に関するものであり、当該化合物が糖尿病の治療及び／又は予防に有用であるとの記載はなく、また、これを示唆する記載もない。
- 10

発明の開示

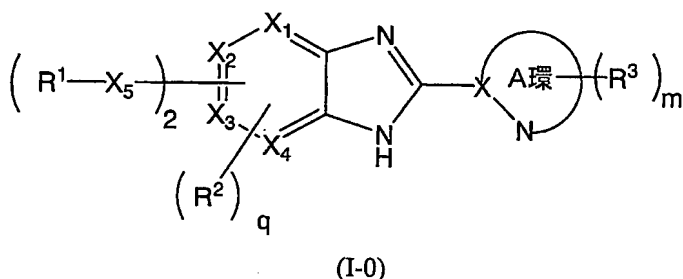
発明が解決しようとする課題

- 本発明の課題は、新規2-ヘテロアリール置換イミダゾール誘導体や、これを用いたグルコキナーゼ活性化剤を提供し、特に、糖尿病、肥満症の治療剤及び／又は予防剤を提供することにある。
- 15

- 本発明者らは、上記既存の薬剤とは異なる作用により、既存の糖尿病薬を上回る薬効を有し、かつ、新たな薬効を有する新規糖尿病薬を開発すべく、鋭意研究した結果、新規2-ヘテロアリール置換ベンズイミダゾール誘導体がグルコキナーゼ活性化作用を有することを見出し、本発明を完成するに至った。
- 20

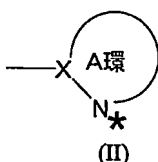
すなわち、本発明は、

(1) 式 (I-0)



[式中、Xは、炭素原子又は窒素原子を示し、

X_1 、 X_2 、 X_3 及び X_4 は、それぞれ独立して、炭素原子又は窒素原子を示し、
A環は、式 (I I)



- 5 で表される窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を環内に1乃至3有していてもよい（式 I I 中の N^* で表される窒素原子は除く）5乃至6員の含窒素芳香族複素環を示すか、或いは、該含窒素芳香族複素環とフェニル又はピリジルとが縮合した双環を示し、

- R^1 は、アリールを示すか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を環内に1乃至4有する4乃至10員の単環の若しくは双環の複素環を示し（該 R^1 は、それぞれ独立して、1乃至3の R^4 で置換されていてもよく、また、該複素環が、脂肪族複素環である場合には、二重結合を1又は2有していてもよい）、
- 10

- R^2 は、それぞれ独立して、ヒドロキシ、ホルミル、 $-\text{CH}_{3-a}\text{F}_a$ 、 $-\text{OCH}_{3-a}\text{F}_a$ 、アミノ、CN、ハロゲン、 C_{1-6} アルキル又は $-(\text{CH}_2)_{1-4}\text{OH}$ を示し、
- 15

- R^3 は、 $-\text{C}_{1-6}$ アルキル、 $-(\text{CH}_2)_{1-6}-\text{OH}$ 、 $-\text{C}(\text{O})-\text{OC}_{1-6}$ アルキル、 $-(\text{CH}_2)_{1-6}-\text{OC}_{1-6}$ アルキル、 $-(\text{CH}_2)_{1-6}-\text{NH}_2$ 、シアノ、 $-\text{C}(\text{O})-\text{C}_{1-6}$ アルキル、ハロゲン、 $-\text{C}_{2-6}$ アルケニル、 $-\text{OC}_{1-6}$ アルキル、 $-\text{COOH}$ 、 $-\text{OH}$ 又はオキソを示し、
- 20

- R^4 は、それぞれ独立して、
 $-\text{C}_{1-6}$ アルキル（該アルキルは、同一又は異なる、1乃至3のヒドロキシ、ハロゲン、 $-\text{OC}(\text{O})-\text{C}_{1-6}$ アルキル（該アルキルは1乃至3のハロゲンで置換されていてもよい）又は $-\text{OC}_{1-6}$ アルキルで置換されていてもよい）、
 25 $-\text{C}_{3-7}$ シクロアルキル、
 $-\text{C}_{2-6}$ アルケニル、
 $-\text{C}(\text{O})-\text{N}(\text{R}^{51})\text{R}^{52}$ 、

- $-S(O)_2-N(R^{51})R^{52}$ 、
 $-O-C_{1-6}$ アルキル（該 C_{1-6} アルキルは、ハロゲン又は $N(R^{51})R^{52}$ で置換されていてもよい）、
 $-S(O)_{0-2}-C_{1-6}$ アルキル、
 5 $-C(O)-C_{1-6}$ アルキル（該 C_{1-6} アルキルは、ハロゲン、アミノ、CN、ヒドロキシ、 $-O-C_{1-6}$ アルキル、 $-CH_{3-a}F_a$ 、 $-OC(O)-C_{1-6}$ アルキル、 $-N(C_{1-6}アルキル)C(O)O-C_{1-6}$ アルキル、 $-NH-C(O)O-C_{1-6}$ アルキル、フェニル、 $-N(R^{51})R^{52}$ 、 $-NH-C(O)-C_{1-6}$ アルキル、 $-N(C_{1-6}アルキル)-C(O)-C_{1-6}$ アルキル又は $-NH-S$
 10 $(O)_{0-2}-C_{1-6}$ アルキルで置換されていてもよい）、
 $-C(S)-C_{3-7}$ シクロアルキル、
 $-C(S)-C_{1-6}$ アルキル、
 $-C(O)-O-C_{1-6}$ アルキル、
 $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$ 、
 15 $-N(R^{53})-C(O)-O-R^{54}$ 、
 $-C(O)-$ アリール（該アリールは、ハロゲンで置換されていてもよい）、
 $-C(O)-$ 芳香族複素環、
 $-C(O)-$ 脂肪族複素環、
 複素環（該複素環は、 $-C_{1-6}$ アルキル（該 $-C_{1-6}$ アルキルは、ハロゲン又は
 20 $-O-C_{1-6}$ アルキルで置換されていてもよい））、
 フェニル（該フェニルは、ハロゲン、 $-C_{1-6}$ アルキル、 $-O-C_{1-6}$ アルキルで置換されていてもよい）、
 ハロゲン、CN、ホルミル、COOH、アミノ、オキソ、ヒドロキシ、ヒドロキシアミノ又はニトロを示し、
 25 R^{51} 及び R^{52} は、それぞれ独立して、水素原子、 $-C_{1-6}$ アルキルを示すか、
 或いは、窒素原子、 R^{51} 及び R^{52} が一緒になって形成する4乃至7員の複素環を示し、
 R^{53} は、水素原子又は $-C_{1-6}$ アルキルを示し、
 R^{54} は、 $-C_{1-6}$ アルキルを示すか、或いは、

R^{53} 及び R^{54} のアルキルと $-N-C(O)-$ とが一緒になって形成する4乃至7員の含窒素脂肪族複素環又は

R^{53} 及び R^{54} のアルキルと $-N-C(O)-O-$ とが一緒になって形成する4乃至7員の含窒素脂肪族複素環（該脂肪族複素環は、オキソで置換されていて
5 もよく、また、該脂肪族複素環は、環内に二重結合を1又は2有していてもよい）を示し、

X_5 は、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 、単結合又は $-O-C_{1-6}$ -アルキルを示し、

a は、それぞれ独立して、1、2又は3の整数を示し、

10 q は、0乃至2の整数を示し、

m は、0乃至2の整数を示す。] で表される化合物（ただし、 X_5 の一方が $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ であり、 X_5 の他方が単結合であって、かつ、 R^1 がアリール又は窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する含窒素芳香族複素環（該アリール
15 又は1乃至3の R^4 で置換されていてよい）である場合、 X_5 が共に単結合である場合、或いは、 R^1 が共に脂肪族複素環である場合を除く）又はその薬学的に許容される塩に関する。

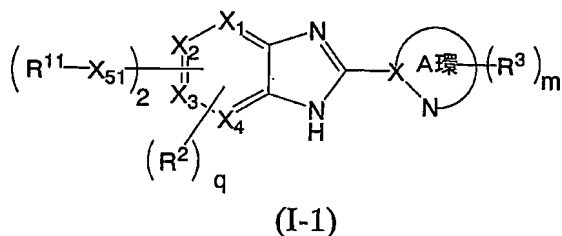
また、本発明は、

(2) 式(I-0)中、 X_1 乃至 X_4 が全て炭素原子である前記(1)記載の化合物又はその薬学的に許容される塩や、
20

(3) 式(I-0)中、 X_5 が $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 又は単結合である前記(1)記載の化合物又はその薬学的に許容される塩に関する。

また、本発明は、

25 (4) 式(I-0)で表される化合物が、式(I-1)



式中、 R^{11} は、1乃至3の R^4 で置換されていてもよいフェニルであるか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）を示し、かつ、 X_{51} が—O—、—S—、—S(O)—又は—S(O)₂—

を示し、他の記号は前記に同じ]である前記(1)記載の化合物又はその薬学的に許容される塩に関する。

また、本発明は、

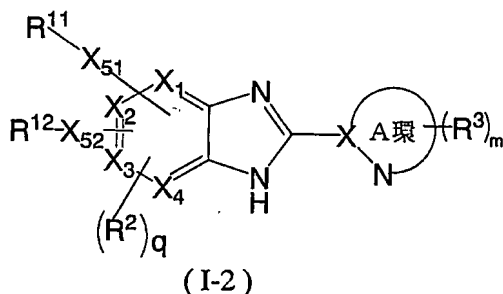
(5) 式(I-1)中、 R^{11} が共に、1乃至3の R^4 で置換されていてもよいフェニルである前記(4)記載の化合物又はその薬学的に許容される塩や、

(6) 式(I-1)中、 R^{11} が共に、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）である前記(4)記載の化合物又はその薬学的に許容される塩や、

(7) 式(I-1)中、 R^{11} の一方が、1乃至3の R^4 で置換されていてもよいフェニルであり、かつ、 R^{11} の他方が、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）である前記(4)記載の化合物又はその薬学的に許容される塩に関する。

また、さらに、本発明は、

(8) 式(I-0)が、式(I-2)



[式中、

R^{11} は、1乃至3の R^4 で置換されていてもよいフェニルであるか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至

4 有する 5 又は 6 員の含窒素芳香族複素環（該含窒素芳香族複素環は、1 乃至 3 の R^4 で置換されていてもよい）を示し、

R^{12} は、複素環を構成するヘテロ原子として、少なくとも窒素原子を 1 つ有し、かつ、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より
5 選択されるヘテロ原子を 1 乃至 4 有していてもよい 4 乃至 7 員の含窒素複素環（該 R^{12} は、1 乃至 3 の R^4 で置換されていてもよく、また、該複素環が、脂肪族複素環である場合には、二重結合を 1 又は 2 有していてもよい）であり、

X_{51} が $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ であり、

X_{52} が $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 又は単結合であり、他の

10 記号は前記に同じ] で表される化合物又はその薬学的に許容される塩に関する。

また、さらに、本発明は、

（9）式（I-2）中、 R^{12} が、複素環を構成するヘテロ原子として、少なくとも窒素原子を 1 つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を 1 乃至 2 有していてもよい 4 乃至

15 7 員の飽和の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1 乃至 3 の R^4 で置換されていてもよい）であり、かつ、 X_{52} が単結合であるか、或いは、 R^{12}

が、複素環を構成する原子として、少なくとも窒素原子を 1 つ有し、かつ、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を 1 乃至 2 有していてもよく、また、環内に二重結合を 1 又は

20 2 有する 5 乃至 7 員の含窒素脂肪族複素環（該 5 乃至 7 員の複素環は、1 乃至 3 の前記 R^4 で置換されていてもよい）であり、かつ、 X_{52} が、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ である前記（8）記載の化合物又はその薬学的に許容される塩や、

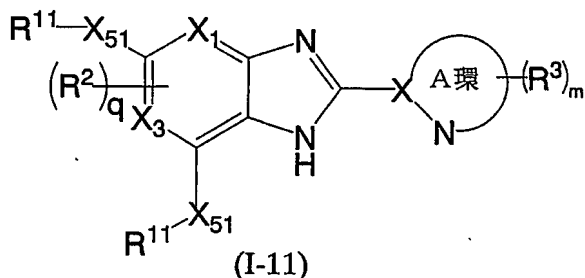
（10）式（I-2）中、 R^{12} が、複素環を構成するヘテロ原子として、少なくとも窒素原子を 1 つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び
25 酸素原子からなる群より選択されるヘテロ原子を 1 乃至 2 有していてもよい 4 乃至 7 員の飽和の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1 乃至 3 の R^4 で置換されていてもよい）であり、かつ、 X_{52} が単結合である前記（8）記載の化合物又はその薬学的に許容される塩や、

(11) 式 (I-2) 中、 R^{12} が、複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環（該5乃至7員の複素環は、1乃至3の前記 R^4 で置換されていてもよい）であり、かつ、 X_{52} が、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ である前記(8)記載の化合物又はその薬学的に許容される塩や、

(12) 式 (I-2) 中、 R^{12} が、複素環を構成するヘテロ原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1乃至3の R^4 で置換されていてもよい）であり、かつ、 X_{52} が、 $-O-$ である前記(8)記載の化合物又はその薬学的に許容される塩に関する。

15 また、さらに、本発明は、

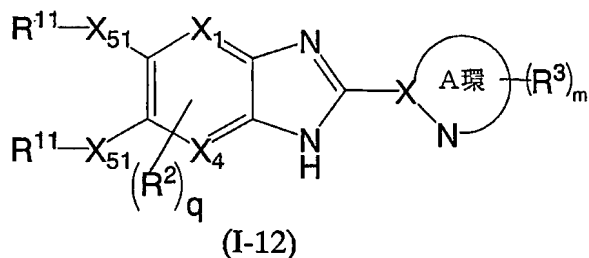
(13) 式 (I-1) が、式 (I-11)



〔式中、各記号は前記に同じ〕で表される化合物又はその薬学的に許容される塩や、

20 (14) 式 (I-12) 中の X_{51} が共に $-O-$ である前記(13)記載の化合物又はその薬学的に許容される塩や、

(15) 式 (I-1) が、式 (I-12)

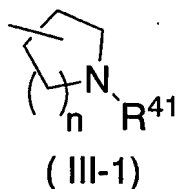


〔式中、各記号は前記に同じ〕で表される化合物又はその薬学的に許容される塩や、

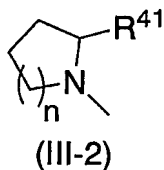
(16) 式 (I-12) 中の X_{51} が、共に $-O-$ である前記 (15) 記載の化合物又はその薬学的に許容される塩に関する。

また、本発明は、

(17) 式 (I-2) 中の R^{12} が、式 (III-1)



又は式 (III-2)



10

〔式中、 n は、1 乃至 3 の整数を示し、 R^{41} は、前記 R^4 と同じ基を意味する〕である前記 (10) 記載の化合物又はその薬学的に許容される塩に関する。

また、本発明は、

(18) A環が、1 乃至 3 の前記 R^4 で置換されていてもよい、チアゾリル、イミダゾリル、イソチアゾリル、チアジアゾリル、オキサジアゾリル、トリアゾリル、オキサゾリル、イソキサゾリル、ピラジニル、ピリジル、ピリダジニル、ピラゾリル又はピリミジニルである前記 (1) 乃至 (17) のいずれか 1 つに記載の化合物又はその薬学的に許容される塩に関する。

また、本発明は、

20 (19) 式 (I-0) で表される化合物が、

- 5 - (4-メタンスルホニル-フェノキシ) - 2-ピラジン-2-イル-6-(2-カルバモイル-フェノキシ) - 1H-ベンズイミダゾール、
- 5 - (2-カルバモイル-フェノキシ) - 2-ピリジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダ
5 ゾール、
- 5 - (2-カルバモイル-フェノキシ) - 2-ピラジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダ
ゾール、
- 5 - (2-フルオロ-フェノキシ) - 2-ピリジン-2-イル-6-(6-メ
10 タンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6-(6-メ
タンスルホニル-ピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1
H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6-(6-メ
15 タンスルホニル-ピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1
H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6-(6-メ
タンスルホニル-ピリジン-3-イルオキシ) - 2-(1-メチル-1H-ピ
ラゾール-3-イル) - 1H-ベンズイミダゾール、
- 20 5 - (2-シアノ-フェノキシ) - 2-ピリジン-2-イル-6-(6-エタ
ンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2-フルオロ-フェノキシ) - 2-ピリジン-2-イル-6-(6-エ
タンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2-フルオロ-フェノキシ) - 2-(1H-ピラゾール-3-イル) -
25 6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイ
ミダゾール、
- 5 - (2, 3-ジフルオロ-フェノキシ) - 2-(1-メチル-1H-ピラ
ゾール-3-イル) - 6-(6-エタンスルホニル-ピリジン-3-イルオキ
シ) - 1H-ベンズイミダゾール、

- 5 - (2, 4-ジフルオロ-フェノキシ) - 2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2, 5-ジフルオロ-フェノキシ) - 2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2, 6-ジフルオロ-フェノキシ) - 2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 10 5 - (2, 6-ジフルオロ-フェノキシ) - 2-(1-メチル-1H-ピラゾール-3-イル) - 6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2-フルオロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 15 5 - (2-フルオロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 5 - (2-クロロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 20 5 - (2-クロロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 5 - (2-シアノピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 25

- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (6-エ
タンスルホニル-ピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1
H-ベンズイミダゾール、
- 5 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (6-エ
タンスルホニル-ピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1
H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (4-エ
タンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1 H-ベンズイミ
ダゾール、
- 10 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (4-エ
タンスルホニル-フェノキシ) - 2-ピラジン-2-イル-1 H-ベンズイミ
ダゾール、
- 5 - (2, 6-ジフルオロ-フェノキシ) - 2-ピリジン-2-イル-6 -
(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイミダ
15 ゾール、
- 5 - (2-カルバモイル-フェノキシ) - 2-ピリジン-2-イル-6 -
(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイミダ
ゾール、
- 5 - (2-フルオロ-6-シアノ-フェノキシ) - 2-ピリジン-2-イル-
20 6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイ
ミダゾール、
- 5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピリジン-2-
イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベ
ンズイミダゾール、
- 25 5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピラジン-2-
イル-6 - (4-エタンスルホニル-フェノキシ) - 1 H-ベンズイミダゾー
ル、

- 5 - (2-フルオロ-6-シアノ-フェノキシ) - 2-ピラジン-2-イル-
6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイ
ミダゾール、
- 5 - (2-フルオロ-6-(テトラゾール-5-イル)-フェノキシ) - 2-
5 ピラジン-2-イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキ
シ) - 1H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシピリジン-3-イルオキシ) - 6 - (3-クロ
ロ-4-メタンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1H-
ベンズイミダゾール、
- 10 4 - (2-フルオロ-フェノキシ) - 2 - (ピリジン-2-イル) - 6 -
(4-メタンスルホニル-フェノキシ) - 1H-ベンズイミダゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-メタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダ
ゾール、
- 15 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-メタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダ
ゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダ
20 ゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダ
ゾール、
- 4 - (1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキ
25 シ) - 6 - (4-エタンスルホニル-フェノキシ) - 2-ピリジン-2-イ
ル-1H-ベンズイミダゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2 - (1H-ピラゾール-3-イル) - 1H-ベ
ンズイミダゾール、

4 - (2 - フルオロ - フェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール、
 4 - (2, 3 - ジフルオロ - フェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダ
 5 ザール、

4 - (2, 5 - ジフルオロ - フェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダ
 ザール、

4 - (2 - シアノ - 6 - フルオロ - フェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイ
 10 ミダゾール

4 - (2 - シアノ - 6 - フルオロ - フェノキシ) - 6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイ
 ミダゾール、

15 4 - (2 - シアノ - 6 - フルオロ - フェノキシ) - 6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイ
 ミダゾール、

1 - (2 - (6 - (5 - ブロモ - ピリジン - 2 - イルオキシ) - 2 - ピリジン - 2 - イル - 3H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
 20 ル) - エタノン、

1 - (2 - (6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 3H - ベンズイミダゾール - 5 - イル) - ピロリジ
 ン - 1 - イル) - エタノン、

1 - (2 - (6 - (4 - ヒドロキシメチル - フェノキシ) - 2 - ピリジン - 2 - イル - 3H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
 25 ル) - エタノン、

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
 ル) - エタノン、

2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イ
ル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - カルボキサミ
ド、

2 - ヒドロキシ - 1 - (2 - (6 - (4 - メタンスルホニル - 1 - フェノキ
5 シ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピ
ロリジン - 1 - イル) - エタノン、

1 - (2 - (6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
ン - 1 - イル) - エタノン、

10 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピラジン -
2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - エタノン、

2 - フルオロ - 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
15 ン - 1 - イル) - エタノン、

5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 - イ
ル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - ピリジン - 2 - カルボニ
トリル、

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン -
20 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - 2 - メチルアミノ - エタノン、

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - (1 H - ピラ
ゾール - 3 - イル) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン -
1 - イル) - エタノン、

25 1 - (4 - フルオロ - 2 - (6 - (4 - メタンスルホニル - フェノキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
ン - 1 - イル) - エタノン、

N - (5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン -
2 - イル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - ピリジン - 2 - イ

ル) - アセタミド、

1 - (2 - (2 - (5 - プロモ - ピリジン - 2 - イル) - 6 - (4 - メタンスルホニル - フェノキシ) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、

- 5 N - (2 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - 2 - オキソ - エチル) - アセタミド、

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (メトキシメチル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - トリ

- 10 フルオロ酢酸塩、

1 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) ピリジン - 2 (1 H) - オン、

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (5 - メチル -

- 15 [1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、

(2 - (2 - (5 - ((2' - フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 6 - イル) ピロリジン - 1 - イル) - 2 - オキソエチル) メチルアミン、

- 20 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - ([1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピラジン - 2 - イル - 1 H -

- 25 ベンズイミダゾール、
- 5 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 6 - (4 - (メタンスルホニル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (2 - メチル - 2

- H-テトラゾール-5-イル) ピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 6-(1-アセチルピロリジン-2-イル) -5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-
 5 ベンズイミダゾール、
- 5-(1-アセチル-5-メチルピロリジン-2-イル) -6-(4-(メタンスルホニル) フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 6-(1-アセチルピロリジン-2-イル) -5-(6-(2-メチル-2H-テトラゾール-5-イル) ピリジン-3-イル) オキシ) -2-ピラジン-2-イル-1H-ベンズイミダゾール、
 10 6-(1-アセチルピロリジン-2-イル) -5-(6-(メトキシメチルピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 15 2-(2-(5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル) ピロリジン-1-イル) -2-オキソエタノール、
- 2-(5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル) ピロリジン-1-カルボキサミド、
 20 5'-(6-(1-アセチルピロリジン-2-イル) -2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル) オキシ) -2H-1, 2'-ビピリジン-2-オン、
- 3-(4-(6-(1-アセチルピロリジン-2-イル) -2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル) オキシ) フェニル) -1, 3-オキサゾリジン-2-オン、
 25 6-(1-アセチルピロリジン-2-イル) -5-(6-メチルピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、

- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - ピラジン - 2 - イルピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダゾール、
- 6 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 5 - ((2' - フルオロピフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダゾール、
- 3 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) - 1, 3 - オキサゾリジン - 2 - オン、
- 10 6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 5 - ((6 - ピラジン - 2 - イルピリジン - 3 - イル) オキシ) - 1H - ベンズイミダゾール、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール、
- 15 1 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) エタノン、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) フェノキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール、
- 20 6 - (1 - アセチル - 5 - メチルピロリジン - 2 - イル) - 5 - (4 - メタン スルホニル - フェノキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール、
- 25 N - メチル - 2 - (2 - (5 - (4 - (2 - メチル - 2H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダゾール - 6 - イル) ピロリジン - 1 - イル) - 2 - オキソエタンアミン、
- 6 - (1 - アセチル - 5 - メチルピロリジン - 2 - イル) - 5 - ((6 - (メトキシメチル) ピリジン - 3 - イル) オキシ) - 2 - ピラジン - 2 - イル - 1

H-ベンズイミダゾール、

1 - (1 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 2 - イル) - エタノン、

- 5 1 - (1 - (6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 2 - イル) - エタノン、

1 - (1 - (6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ

- 10 ン - 2 - イル) - エタノン若しくは

1 - (1 - (6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - 4 - フルオロ - ピロリジン - 2 - イル) - エタノンである化合物又はその薬学的に許容される塩に関する。

- 15 また、さらに、本発明は、

(20) 2 型糖尿病の治療、予防及び／又は発症を遅らせるために用いられる以下の (1) - (3) からなる医薬組成物

(1) 前記 (1) 乃至 (19) のいずれか 1 つに記載の化合物、

(2) 以下の (a) - (h) からなる群より選択される 1 又は 2 以上の化合物

- 20 (a) 他のグルコキナーゼ活性化剤

(b) ビス - グアニド

(c) PPAR アゴニスト

(d) インスリン

(e) ソマトスタチン

- 25 (f) α - グルコシダーゼ 阻害剤

(g) インスリン、及び

(h) DPP - IV (ジペプチジルペプチダーゼ IV) 阻害剤

(3) 薬学的に許容される担体や、

(21) 前記 (1) 乃至 (19) のいずれか 1 つに記載の化合物又はその薬学

的に許容される塩を有効成分とするグルコキナーゼ活性化剤や、

(22) 前記(1)乃至(20)のいずれか1つに記載の化合物又はその薬学的に許容される塩を有効成分とする糖尿病の治療及び／又は予防のための薬剤や、

- 5 (23) 前記(1)乃至(20)のいずれか1つに記載の化合物又はその薬学的に許容される塩を有効成分とする肥満の治療及び／又は予防剤、に関する。

発明を実施するための最良の形態

- 以下に本明細書において用いられる用語の意味について説明し、本発明に係
10 る化合物についてさらに詳細に説明する。

本明細書において、特に断りがない限り、下記の基としては、以下のものを具体的に挙げることができる。

- 「アリール」とは、好ましくは、炭素数6乃至14の炭化水素芳香環を意味し、例えばフェニル、ナフチル、ビフェニル、アントリル等が挙げられ、これ
15 らのうち、フェニル、ナフチル又はビフェニルが好ましく、フェニルがより好ましい。

- 「C₁₋₆アルキル」とは、直鎖又は分岐を有する炭素数1乃至6のアルキルを意味し、例えば、メチル、エチル、プロピル、イソプロピル、ブチル、イソブチル、sec-ブチル、tert-ブチル、ペンチル、イソアミル、ネオペンチル、イソペンチル、1, 1-ジメチルプロピル、1-メチルブチル、2-メチルブチル、1, 2-ジメチルプロピル、ヘキシル、イソヘキシル、1-メチルペンチル、2-メチルペンチル、3-メチルペンチル、1, 1-ジメチルブチル、1, 2-ジメチルブチル、2, 2-ジメチルブチル、1, 3-ジメチルブチル、2, 3-ジメチルブチル、3, 3-ジメチルブチル、1-エチルブチル、2-エチルブチル、1, 2, 2-トリメチルプロピル、1-エチル-2-メチルプロピル等が挙げられる。
20
25

「C₂₋₆アルケニル」とは、直鎖又は分岐を有する炭素数2乃至6のアルケニルを意味し、例えば、アリル、2-プロペニル、1-ブテニル、2-ブテニル、2-メチル-2-ブテニル、1-ペンテニル等が挙げられる。

「 C_{3-7} シクロアルキル」とは、具体的には、例えば、シクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル、シクロヘプチル等が挙げられる。

「ハロゲン」とは、フッ素、塩素、臭素又はヨウ素を意味する。

「 $-(CH_2)_{1-6}-OH$ 」としては、例えば、ヒドロキシメチレン、ヒドロキシエチレン等が挙げられる。

「 $-O-C_{1-6}$ アルキル」としては、例えば、メトキシ、エトキシ、プロポキシ又はtert-ブトキシ等が挙げられる。

「 $-(CH_2)_{1-6}-OC_{1-6}$ アルキル」としては、例えば、メトキシメチル、メトキシエチル、プロピルオキシメチル、イソプロピルオキシメチル等が挙げられる。

「 $-C(O)-_{1-6}$ アルキル」としては、例えば、アセチル、エチルカルボニル、イソプロピルカルボニル、プロピルカルボニル等が挙げられる。

「 $-C(O)OC_{1-6}$ アルキル」としては、例えば、メトキシカルボニル、エトキシカルボニル又はtert-ブトキシカルボニル等が挙げられる。

「 $-(CH_2)_{1-6}-NH_2$ 」としては、例えば、アミノメチル、アミノエチル、アミノプロピル等が挙げられる。

「 $-NH-C_{1-6}$ アルキル」としては、例えば、メチルアミノ、エチルアミノ、プロピルアミノ又は2-メチルブチル-アミノ等が挙げられる。

「 $-N-ジ-(C_{1-6}$ アルキル)」とは、同一又は異なる前記定義の「 C_{1-6} アルキル」とNとが結合した基を意味し、例えば、ジメチルアミノ、エチルプロピルアミノ、2-メチルブチル-1-メチルアミノ等が挙げられる。また、

「 $-N-ジ-(C_{1-6}$ アルキル)」中の同一又は異なる C_{1-4} アルキルが窒素原子と一緒にあって、環を形成していてもよく、該環の具体例としては、例えば、ピペリジン、ピロリジン等が挙げられる。

「 $-CH_{3-a}F_a$ 」は、メチル中の1乃至3の水素原子がフッ素原子で置換された基を意味し、例えば、トリフルオロメチル、ジフルオロメチル又はフルオロメチル等が挙げられる。

「 $-OCH_{3-a}F_a$ 」は、前記定義の「 $-CH_{3-a}F_a$ 」と酸素原子とが結合した基を意味し、例えば、トリフルオロメトキシ、ジフルオロメトキシ又はフル

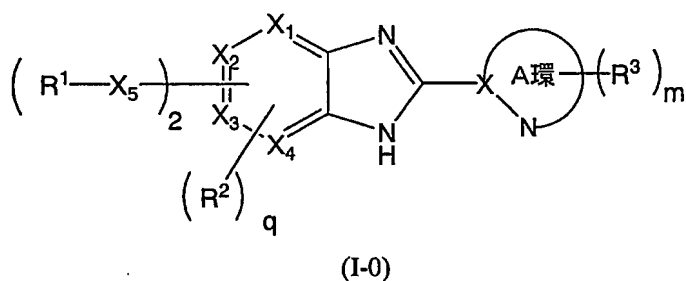
オロメトキシ等が挙げられる。

a は、1 乃至 3 の整数を示す。

本発明に係る化合物について更に具体的に開示するために、式 (I-0)、
(I-1)、(I-2)、(I-11) 又は (I-12) において用いられる

5 各種記号について、具体例を挙げて説明する。

本発明に係る式 (I-0)



で表される化合物について説明する。

X_5 は、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 、単結合又は $-O-$
10 C_{1-6} -アルキルを示す。

R^1 は、アリールを示すか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を環内に 1 乃至 4 有する単環の又は双環の 4 乃至 10 員の含窒素複素環を示す。

R^1 が示す「アリール」とは、前記定義のアリールと同様の基が挙げられ、
15 フェニル、ナフチル又はビフェニルが好ましく、フェニルがより好ましい。

R^1 が示す「窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を環内に 1 乃至 4 有する 4 乃至 7 員の単環又は 9 若しくは 10 員の縮合した複素環」とは、複素環の環構成原子のうちの 1 乃至 4 が、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子であり、複素環構成原子の他の原子が炭素原子であって、環全体として 4 乃至 7 員環を構成する単環の若しくは 9 若しくは 10 員環を構成する双環の脂肪族複素環又は芳香族複素環を意味する。
20

該複素環内に窒素原子を有する場合には、該窒素原子は、N-オキサイドを形成していてもよい。

25 該複素環内にヘテロ原子が 2 又は 3 有する場合には、これらは同一又は異

なっているもよい。

該複素環が、脂肪族複素環である場合には、該複素環内に二重結合を1又は2有しているもよい

該複素環が、脂肪族複素環である場合には、また、該複素環中のメチレンが、
5 窒素原子、硫黄原子又は酸素原子で置き換わっているもよく、さらに、該硫黄原子は、酸化されてスルフェニル又はスルホニルとなっているもよい。

該複素環としては、例えば、アゼチジニル、チアゾリジニル、ピロリジニル、
ピロリニル、2-ピロリドニル、アゼパニル、2, 5-ジオキソピロリジニル、
2-ベンゾオキサリノニル、1, 1-ジオキソテトラヒドロチエニル、2,
10 4-ジオキソイミダゾリジニル、2-オキソ-[1, 3, 4]- (4-トリアゾリニル)、
2-オキサゾリジノニル、5, 6-ジヒドロウラシリル、1,
3-ベンゾジオキサリル、[1, 2, 4]-オキサジアゾリニル、2-アザビシクロ[2. 2. 1]ヘプチル、4-チアゾリドニル、モルホリノ、2-オキソテトラヒドロフラニル、テトラヒドロフラニル、2, 3-ジヒドロベン
15 フラニル、ベンゾチエニル、イソキサゾリル、テトラヒドロピラニル、ピペリ
ジニル、1-オキソ-1, 3-ジヒドロイソインドリル、ピペラジニル、チオモ
ルホリノ、1, 1-ジオキソチオモルホリノ、テトラヒドロピラニル、1,
3-ジオキサラニル、ホモピペラジニル、チエニル、イソオキサゾリル、イミ
ダゾリル、ピロリル、チアゾリル、チアジアゾリル、イソチアゾリル、[1,
20 2, 4]-トリアゾリル、[1, 2, 3]-トリアゾリル、ピラニル、インド
リル、ピリミジニル、チアゾリル、ピラジニル、ピリダジニル、ピリジニル、
4-ピリドニル、キノリル又はイソキノリニルが挙げられる。

これらのうち、4乃至7員の単環の複素環としては、具体的には、例えば、
アゼチジニル、イソキサゾリル、ピロリジニル、2-ピロリドニル、2, 5-
25 ジオキソピロリドニル、モルホリノ、テトラヒドロフラニル、アゼパニル、ヒ
ペリジニル、ピペラジニル、チオモルホリノ、テトラヒドロピラニル、イミダ
ゾリル、トリアゾリル、オキサジアゾリル、テトラゾリル、ピラゾリル、インド
リル、チアゾリル、チアジアゾリル、ピラジニル、ピリダジニル又はピリジニル
等が挙げられる。

これらのうち、4乃至7員の単環の脂肪族複素環としては、具体的には、例えば、アゼチジニル、ピロリジニル、ピペリジノ、ピペリジニル、アゼパニル、ピペラジニル、モルホリノ、チオモルホリノ、ホモピペラジニル、イミダゾリジニル、ピラゾリジニル等が挙げられる。

- 5 これらのうち、5又は6員の単環の芳香族複素環としては、具体的には、例えば、ピロリル、フリル、チエニル、ピラゾリル、イソキサゾリル、イソチアゾリル、イミダゾリル、オキサゾリル、チアゾリル、トリアゾリル、オキサジアゾリル、チアジアゾリル、テトラゾリル、ピリジル、ピラジニル、ピリミジニル、ピリダジニル等が挙げられる。
- 10 これらのうち、9又は10員の縮合した複素環としては、具体的には、例えば、ベンゾフラニル、ベンゾイミダゾリル、ベンゾチオフェニル、ベンゾチアゾリル、ベンゾイソチアゾリル、ベンゾオキサゾリル、ベンゾイソオキサゾリル、ピリドイミダゾリル、キノリル、イソキノリル、キノキサリニル、キナゾリニル、フタラジニル、シンノリニル、インドリル、インダゾリル、プリニル、
- 15 インドリジニル、イソインドリル、プテリジニル又はナフチリジニル等が挙げられる。

該複素環としては、該複素環構成原子の少なくとも1つが窒素原子である4乃至7員の単環の脂肪族複素環又は5若しくは6員の芳香族複素環が好ましい。

R^1 は、1乃至3の R^4 で置換されていてもよい。

- 20 ここで、 R^4 は、それぞれ独立して、 $-C_{1-6}$ アルキル（該アルキルは、同一又は異なる、1乃至3のヒドロキシ、ハロゲン、 $-OC(O)-C_{1-6}$ アルキル（該アルキルは1乃至3のハロゲンで置換されていてもよい）又は $-OC_{1-6}$ アルキルで置換されていてもよい）、
- $-C_{3-8}$ シクロアルキル、
- 25 $-C_{2-6}$ アルケニル、
- $-C(O)-N(R^{51})R^{52}$ 、
- $-S(O)_2-N(R^{51})R^{52}$
- $-O-C_{1-6}$ アルキル（該 C_{1-6} アルキルは、ハロゲン又は $N(R^{51})R^{52}$ で置換されていてもよい）、

- $-S(O)_{0-2}-C_{1-6}$ アルキル、
 $-C(O)-C_{1-6}$ アルキル（該 C_{1-6} アルキルは、ハロゲン、アミノ、CN、
 ヒドロキシ、 $-O-C_{1-6}$ アルキル、 $-CH_{3-a}F_a$ 、 $-OC(O)-C_{1-6}$ アル
 キル、 $-N(C_{1-6}$ アルキル) $C(O)O-C_{1-6}$ アルキル、フェニル、 $-N$
 5 $(R^{51})R^{52}$ 、 $-NH-C(O)-C_{1-6}$ アルキル、 $-N(C_{1-6}$ アルキル) $-$
 $C(O)-C_{1-6}$ アルキル又は $-NH-S(O)_{0-2}C_{1-6}$ アルキルで置換され
 ていてもよい）、
 $-C(O)-C_{3-8}$ シクロアルキル、
 $-C(S)-C_{1-6}$ アルキル、
 10 $-C(O)-O-C_{1-6}$ アルキル、
 $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$ 、
 $-N(R^{53})-C(O)-O-R^{54}$ 、
 $-C(O)-$ アリール（該アリールは、ハロゲンで置換されていてもよい）、
 $-C(O)-$ 芳香族複素環、
 15 $-C(O)-$ 複素環、
 複素環（該複素環は、 $-C_{1-6}$ アルキル（該 $-C_{1-6}$ アルキルは、ハロゲン又
 は $-O-C_{1-6}$ アルキルで置換されていてもよい））、
 フェニル（該フェニルは、ハロゲン、 $-C_{1-6}$ アルキル、 $-O-C_{1-6}$ アルキル
 で置換されていてもよい）、
 20 ハロゲン、CN、ホルミル、COOH、アミノ、オキソ、ヒドロキシ、ヒドロ
 キシアミジノ又はニトロを示す。

R^4 が示す「ハロゲン」とは、前記定義と同様の基を意味する。

- R^4 が示す「 $-C_{1-6}$ アルキル」としては、直鎖又は分岐を有する炭素数1乃
 至6のアルキルを意味し、例えば、メチル、エチル、プロピル、イソプロピル、
 25 ブチル、イソブチル、sec-ブチル、tert-ブチル、ペンチル、イソア
 ミル、ネオペンチル、イソペンチル、1, 1-ジメチルプロピル、1-メチル
 ブチル、2-メチルブチル、1, 2-ジメチルプロピル、ヘキシル、イソヘキ
 シル、1-メチルペンチル、2-メチルペンチル、3-メチルペンチル、1,
 1-ジメチルブチル、1, 2-ジメチルブチル、2, 2-ジメチルブチル、1,

3-ジメチルブチル、2, 3-ジメチルブチル、3, 3-ジメチルブチル、
1-エチルブチル、2-エチルブチル、1, 2, 2-トリメチルプロピル、
1-エチル-2-メチルプロピル等が挙げられる。

該「 $-C_{1-6}$ アルキル」は、1乃至3のヒドロキシ、ハロゲン、 $-OC$
5 (O) $-C_{1-6}$ アルキル(該アルキルは、1乃至3のハロゲンで置換されていて
もよい)又は $-O-C_{1-6}$ アルキルで置換されていてよい。

該「 $-C_{1-6}$ アルキル」が、上記置換基を2又は3有する場合には、これらは、
同一又は異なっていてよい。

該置換基のハロゲンとは、前記定義のハロゲンと同様の基が挙げられる。

10 該置換基の $-OC(O)-C_{1-6}$ アルキルとしては、例えば、メチルカルボニ
ルオキシ、エチルカルボニルオキシ、イソプロピルカルボニルオキシ等が挙げ
られる。

該置換基の $-OC(O)-C_{1-6}$ アルキルは、前記定義のハロゲン原子で1乃
至3置換されていてよい。

15 該置換基の $-O-C_{1-6}$ アルキルとしては、例えば、メトキシ、エトキシ、プ
ロポキシ、イソプロポキシ等が挙げられる。

R^4 が示す「 $-S(O)_{0-2}-C_{1-6}$ アルキル」とは、 $-S(O)_{0-2}-$ と前記
定義の $-C_{1-6}$ アルキルとが結合した基を意味し、例えば、 $-S-$ エチル、 $-$
 $S-$ メチル、 $-S-$ イソプロピル、 $-S-$ プロピル、 $-S(O)_2-$ メチル、 $-$
20 $S(O)_2-$ エチル等が挙げられる。

該「 $-S(O)_{0-2}-C_{1-6}$ アルキル」中の $-C_{1-6}$ アルキルは、ヒドロキシ
で置換されていてよい。

R^4 が示す「 $-C_{3-8}$ シクロアルキル」としては、前記定義と同様の基が挙げ
られる。

25 R^4 が示す「 $-C_{2-6}$ アルケニル」としては、前記定義と同様の基が挙げられ
る。

R^4 が示す「 $C(O)N(R^{51})R^{52}$ 」とは、置換された又は無置換のカルバ
モイル基を意味するか、或いは、N、 R^{51} 及び R^{52} が一緒になって形成する4
乃至7員の脂肪族複素環とカルボニルとが結合した基を意味する。

R^4 が示す「 $C(O)N(R^{51})R^{52}$ 」のうち、置換された又は無置換の置換カルバモイルとしては、例えば、カルバモイル、メチルカルバモイル、エチルカルバモイル、イソプロピルカルバモイル、プロピルカルバモイル、エチルメチルカルバモイル、ジメチルカルバモイル、イソプロピルメチルカルバモイル、
5 ジイソプロピルカルバモイル、ジエチルカルバモイル等が挙げられる。

R^4 が示す「 $C(O)N(R^{51})R^{52}$ 」のうちのN、 R^{51} 及び R^{52} が一緒になって形成する4乃至7員の脂肪族とは、具体的には、例えば、アゼチジニル、ピロリジニル、ピペリジノ、ピペラジニル、モルホリノ等が挙げられる。したがって、 $C(O)N(R^{51})R^{52}$ としては、アゼチジン-1-カルボニル、ピ
10 ロリジン-1-カルボニル、ピペリジン-1-カルボニル、ピペラジン-1-カルボニル、モルホリン-1-カルボニル等が挙げられる。

R^4 が示す「 $-C(O)-O-C_{1-6}$ アルキル」としては、前記定義の「 $-C(O)-O-C_{1-6}$ アルキル」と同様の基が挙げられる。

R^4 が示す「 $-O-C_{1-6}$ アルキル」としては、前記定義の「 $-O-C_{1-6}$ アルキル」と同様の基が挙げられる。
15

該 $-O-C_{1-6}$ アルキルは、ハロゲン又は $N(R^{51})R^{52}$ で置換されていてもよい。

R^4 が示す「 $-C(O)-C_{1-6}$ アルキル」としては、前記定義の「 $-C(O)-C_{1-6}$ アルキル」と同様の基が挙げられる。

20 該「 $-C(O)-C_{1-6}$ アルキル」は、ハロゲン、アミノ、 $-CH_{3-a}F_a$ 、CN、ヒドロキシ、 $-O-C_{1-6}$ アルキル、 $-O-C(O)-C_{1-6}$ アルキル、 $-N-(C_{1-6}$ アルキル)- $C(O)O-C_{1-6}$ アルキル、 $-NH-C(O)O-C_{1-6}$ アルキル、フェニル、 $-N(R^{51})R^{52}$ 、 $-NH-C(O)-C_{1-6}$ アルキル、 $-N-(C_{1-6}$ アルキル)- $C(O)-C_{1-6}$ アルキル又は $-NH-S(O)_{0-2}-C_{1-6}$ アルキルで置換されていてもよい。
25

該置換基の「ハロゲン」としては、前記定義のハロゲンと同様の基が挙げられる。

該置換基の「 $-CH_{3-a}F_a$ 」としては、前記定義の「 $-CH_{3-a}F_a$ 」と同様の基が挙げられる。

該置換基の「 $-O-C_{1-6}$ アルキル」としては、前記定義の「 $-O-C_{1-6}$ アルキル」と同様の基が挙げられる。

該置換基の「 $-O-C(O)-C_{1-6}$ アルキル」としては、前記「 $-O-C(O)-C_{1-6}$ アルキル」と同様の基が挙げられる。

- 5 該置換基の「 $-N-(C_{1-6}$ アルキル) $-C(O)O-C_{1-6}$ アルキル」とは、 $-N-(C_{1-6}$ アルキル) $-$ と前記 $-C(O)O-C_{1-6}$ アルキルとが結合した基を意味し、具体的には、例えば、 $-N(Me)-C(O)O-tert-butyl$ 等が挙げられる。

- 10 該置換基の「 $-NH-C(O)O-C_{1-6}$ アルキル」とは、 $-NH-$ と前記 $-C(O)O-C_{1-6}$ アルキルとが結合した基を意味し、具体的には、例えば、 $-NH-C(O)O-Methyl$ 、 $-NH-C(O)O-Ethyl$ 、 $-NH-C(O)O-Isopropyl$ 等が挙げられる。

該置換基の「 $-N(R^{51})R^{52}$ 」としては、前記「 $-N(R^{51})R^{52}$ 」と同様の基が挙げられる。

- 15 該置換基の「 $-NH-C(O)-C_{1-6}$ アルキル」とは、 $-NH-C(O)-$ と前記定義の $-C_{1-6}$ アルキルとが結合した基を意味し、具体的には、例えば、 $-NH-C(O)-Methyl$ 、 $-NH-C(O)-Ethyl$ 、 $-NH-C(O)-Isopropyl$ 等が挙げられる。

- 20 該置換基の「 $-N-(C_{1-6}$ アルキル) $-C(O)-C_{1-6}$ アルキル」とは、 $-N-(C_{1-6}$ アルキル) $-C(O)-$ と前記定義の $-C_{1-6}$ アルキルとが結合した基を意味し、具体的には、例えば、 $-N(Methyl)-C(O)-Methyl$ 、 $-N(Methyl)-C(O)-Ethyl$ 、 $-N(Ethyl)-C(O)-Isopropyl$ 、 $-N(Methyl)-C(O)-Isopropyl$ 、 $-N(Isopropyl)-C(O)-Methyl$ 等が挙げられる。

- 25 該置換基の「 $-NH-S(O)_{0-2}-C_{1-6}$ アルキル」とは、 $-NH-$ と前記 $-S(O)_{0-2}-C_{1-6}$ アルキルとが結合した基を意味し、具体的には、例えば、 $-NH-S(O)_2-Methyl$ 、 $-NH-S(O)_2-Ethyl$ 、 $-NH-S(O)_2-Isopropyl$ 等が挙げられる。

C_{1-6} アルキル上に前記置換基を有していてもよい「 $-C(O)-C_{1-6}$ アル

キル」としては、具体的には、例えば、フルオロメチルカルボニル、2, 2, 2-トリフルオロエチルカルボニル、シアノメチルカルボニル、ヒドロキシメチルカルボニル、2-ヒドロキシエチルカルボニル、メトキシメチルカルボニル、アミノメチルカルボニル、N-メチルアミノカルボニル、2-フェニルエチルカルボニル等が挙げられる。

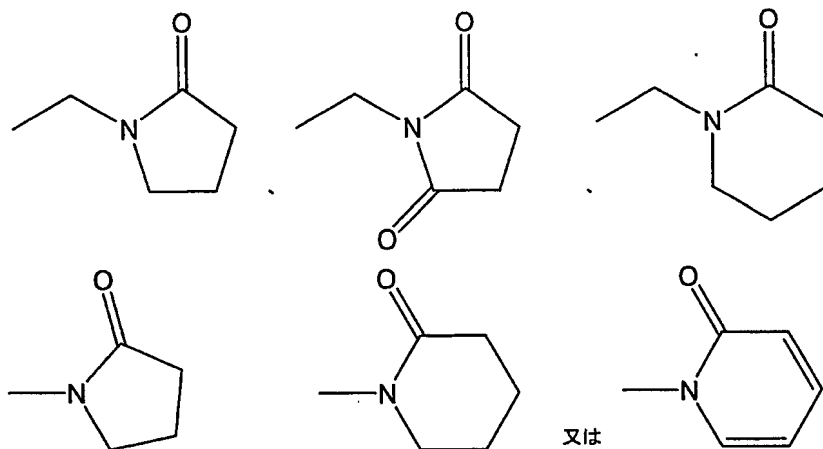
R^4 が示す「 $-C(S)-C_{1-6}$ アルキル」とは、 $-C(S)-$ と前記定義の「 $-C_{1-6}$ アルキル」とが結合した基を意味し、具体的には、例えば、 $-C(S)-$ メチル、 $-C(S)-$ エチル、 $-C(S)-$ イソプロピル、 $-C(S)-$ プロピル等が挙げられる。

10 R^4 が示す「 $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$ 」において、 R^{53} は、水素原子又は $-C_{1-6}$ アルキルを意味し、 R^{54} は、 $-C_{1-6}$ アルキルを意味するか、或いは、「 $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$ 」中の $-N(R^{53})-C(O)-R^{54}$ において、 $-N-C(O)-$ と R^{53} 及び R^{54} のアルキルが一緒になって形成する4乃至7員の含窒素脂肪族複素環（該複素環は、
15 オキソで置換されていてもよく、また、環内に二重結合を1又は2有していてもよい）を意味する。

R^{53} が水素原子又は $-C_{1-6}$ アルキルであり、かつ、 R^{54} は、 $-C_{1-6}$ アルキルである場合の「 $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$ 」としては、具体的には、例えば、 $-CH_2-NH-C(O)-$ メチル、 $-CH_2-NH-C(O)-$ エチル、 $-CH_2-NH-C(O)-$ イソプロピル、 $-CH_2-NH-C(O)-$ プロピル、 $-CH_2-N(メチル)-C(O)-$ メチル、 $-CH_2-N(エチル)-C(O)-$ メチル、 $-NH-C(O)-$ メチル、 $-NH-C(O)-$ エチル、 $-NH-C(O)-$ イソプロピル、 $-NH-C(O)-$ プロピル、 $-N(メチル)-C(O)-$ メチル、 $-N(エチル)-C(O)-$ メチル等
25 が挙げられる。

$-N-C(O)-$ と R^{53} 及び R^{54} の C_{1-6} -アルキルが一緒になって4乃至7員の含窒素脂肪族複素環（該複素環は、オキソで置換されていてもよく、また、環内に二重結合を1又は2有していてもよい）を形成する場合の「 $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$ 」としては、具体的には、例えば、式

(IV)



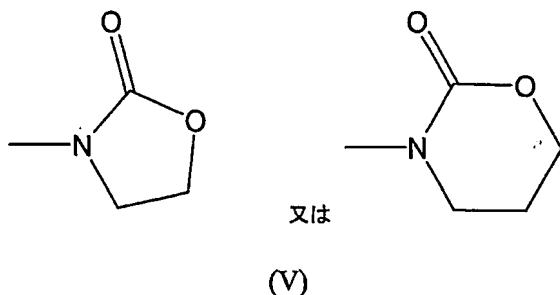
(IV)

で表される基等が挙げられる。

- 5 R^4 が示す「 $-N(R^{55})-C(O)-O-R^{56}$ 」において、 R^{55} は、水素原子又は $-C_{1-6}$ アルキルを意味し、 R^{56} は、 $-C_{1-6}$ アルキルを意味するか、或いは、「 $-N(R^{55})-C(O)-O-R^{56}$ 」中の $-N(R^{55})-C(O)-O-R^{56}$ において、 $-N-C(O)-O-$ と R^{55} 及び R^{56} のアルキルが一緒になって形成する4乃至7員の含窒素脂肪族複素環を意味する。

- 10 R^{55} が水素原子又は $-C_{1-6}$ アルキルであり、かつ、 R^{56} は、 $-C_{1-6}$ アルキルである場合の「 $-N(R^{55})-C(O)-O-R^{56}$ 」としては、具体的には、例えば、 $-NH-C(O)-O-$ メチル、 $-NH-C(O)-O-$ エチル、 $-NH-C(O)-O-$ イソプロピル、 $-NH-C(O)-O-$ プロピル、 $-N$ (メチル) $-C(O)-O-$ メチル、 $-N$ (エチル) $-C(O)-O-$ メチル等が挙げられる。

- 15 $-N-C(O)-O-$ と R^{55} 及び R^{56} の C_{1-6} -アルキルが一緒になって4乃至7員の含窒素脂肪族複素環を形成する場合の「 $-N(R^{53})-C(O)-R^{54}$ 」としては、具体的には、例えば、式(V)



で表される基等が挙げられる。

- R^4 が示す「 $-C(O)-$ アリール」とは、カルボニルと前記定義のアリールとが結合した基を意味し、具体的には、例えば、ベンゾイル、ナフチルカルボ
5 ニル等が挙げられる。

また、該「 $-C(O)-$ アリール」中のアリールは、前記定義のハロゲン原子で、1乃至3置換されていてもよい。

該置換基のハロゲンが、2又は3存在する場合には、これらは、同一又は異なっているともよい。

- 10 R^4 が示す「 $-C(O)-$ 芳香族複素環」とは、カルボニルと前記定義の5若しくは6員の単環の芳香族複素環又は9若しくは10員の双環の芳香族複素環とが結合した基を意味し、具体的には、例えば、 $-C(O)-$ ピロリル、 $-C(O)-$ フリル、 $-C(O)-$ チエニル、 $-C(O)-$ 、 $-C(O)-$ ピラゾ
リル、 $-C(O)-$ イソキサゾリル、 $-C(O)-$ イソチアゾリル、 $-C$
15 $(O)-$ イミダゾリル、 $-C(O)-$ オキサゾリル、 $-C(O)-$ チアゾリ
ル、 $-C(O)-$ トリアゾリル、 $-C(O)-$ オキサジアゾリル、 $-C$
 $(O)-$ チアジアゾリル、 $-C(O)-$ テトラゾリル、 $-C(O)-$ ピリジ
ル、 $-C(O)-$ ピラジニル、 $-C(O)-$ ピリミジニル、 $-C(O)-$ ピリ
ダジニル等が挙げられる。
- 20 R^4 が示す「 $-C(O)-$ 芳香族複素環」とは、カルボニルと前記定義の4乃至7員の単環の脂肪族複素環とが結合した基を意味し、具体的には、具体的には、例えば、 $-C(O)-$ アゼチジニル、 $-C(O)-$ ピロリジニル、 $-C$
 $(O)-$ ピペリジノ、 $-C(O)-$ ピペリジニル、 $-C(O)-$ アゼパニ
ル、 $-C(O)-$ ピペラジニル、 $-C(O)-$ モルホリノ、 $-C(O)-$ チオ
25 モルホリノ、 $-C(O)-$ ホモピペラジニル、 $-C(O)-$ イミダゾリジニ

ル、 $-C(O)-$ ピラゾリジニル等が挙げられる。

R^4 が示す「複素環」とは、 R^1 が示す「複素環」と同様の基が挙げられる。

また、該複素環は、 $-C_{1-6}$ -アルキル、ハロゲン又は $-O-C_{1-6}$ -アルキルで1乃至3置換されていてもよい。

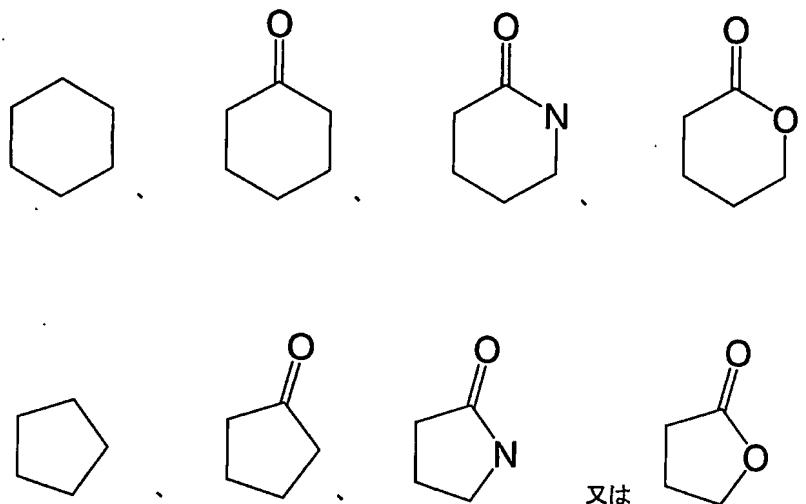
- 5 該置換基が2又は3存在する場合には、これらは、同一又は異なっているもよい。

該置換基の $-C_{1-6}$ -アルキル、ハロゲン及び $-O-C_{1-6}$ -アルキルは、それぞれ、前記定義のものと同様の基が挙げられる。

- 10 R^4 が示す「ハロゲン」としては、前記定義の「ハロゲン」と同様の基が挙げられる。

R^4 が示す「フェニル」は、ハロゲン、 $-C_{1-6}$ -アルキル又は $-O-C_{1-6}$ -アルキルで置換されていてもよい。

- 15 R^1 が置換基として R^4 を2又は3有している場合には、同一又は異なる2つの R^4 が一緒になって、4乃至6員環を形成していてもよく、具体的には、例えば、式(VI)



(VI)

で表される基等が挙げられる。

$-X_5-$ は、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 、単結合又は $-O-C_{1-6}$ -アルキルを示す。

$-X_5-$ としては、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 又は単結合である場合が好ましい。

R^1-X_5- (該 R^1 は、1乃至3の前記の R^4 で置換されていてもよい。)としては、具体的には、例えば、フェニルスルファニル、フェノキシ、ベンジルオキシ、フェネチルオキシ、2-シアノフェノキシ、3-シアノフェノキシ、4-シアノフェノキシ、2-シアノ-6-フルオロフェノキシ、2-カルバモイルフェノキシ、3-カルバモイルフェノキシ、4-カルバモイルフェノキシ、2-フルオロ-6-カルバモイルフェノキシ、2-メチルカルバモイルフェノキシ、3-メチルカルバモイルフェノキシ、4-メチルカルバモイルフェノキシ、2-ジメチルカルバモイルフェノキシ、3-ジメチルカルバモイルフェノキシ、4-ジメチルカルバモイルフェノキシ、2-メトキシフェノキシ、3-メトキシフェノキシ、4-メトキシメチルフェノキシ、2-イソプロピルフェノキシ、3-イソプロピルフェノキシ、4-イソプロピルフェノキシ、2-メチルフェノキシ、3-メチルフェノキシ、4-メチルフェノキシ、2-エチルフェノキシ、3-エチルフェノキシ、4-エチルフェノキシ、2-アセチルフェノキシ、3-アセチルフェノキシ、4-アセチルフェノキシ、2-メタンスルホニルフェノキシ、3-メタンスルホニルフェノキシ、3-クロロ-4-メタンスルホニルフェノキシ、4-メタンスルホニルフェノキシ、2-エタンスルホニルフェノキシ、3-エタンスルホニルフェノキシ、4-エタンスルホニルフェノキシ、2-メトキシカルボニルフェノキシ、3-メトキシカルボニルフェノキシ、4-メトキシカルボニルフェノキシ、2-エトキシカルボニルフェノキシ、3-エトキシカルボニルフェノキシ、4-エトキシカルボニルフェノキシ、2-ヒドロキシフェノキシ、3-ヒドロキシフェノキシ、4-ヒドロキシフェノキシ、2-ヒドロキシメチルフェノキシ、3-ヒドロキシメチルフェノキシ、4-ヒドロキシメチルフェノキシ、2-ヒドロキシエチルフェノキシ、3-ヒドロキシエチルフェノキシ、4-ヒドロキシエチルフェノキシ、2-ホルミルフェノキシ、3-ホルミルフェノキシ、4-ホルミルフェノキシ、2-(1-ヒドロキシエチル)フェノキシ、3-(1-ヒドロキシエチル)フェノキシ、4-(1-ヒドロキシエチル)

- フェノキシ、2、3-ジフルオロフェノキシ、2、5-ジフルオロフェノキシ、
 2、4-ジフルオロフェノキシ、2、6-ジフルオロフェノキシ、2-フルオ
 ロフェノキシ、3-フルオロフェノキシ、4-フルオロフェノキシ、2-ジ
 フルオロメトキシフェノキシ、3-ジフルオロメトキシフェノキシ、4-ジフ
 5 ルオロメトキシフェノキシ、2-トリフルオロメトキシフェノキシ、3-トリ
 フルオロメトキシフェノキシ、4-トリフルオロメトキシフェノキシ、2-
 (1H-テトラゾール-5-イル) フェノキシ、3- (1H-テトラゾール-
 5-イル) フェノキシ、4- (1H-テトラゾール-5-イル) フェノキシ、
 4- (2-メチル-2H-テトラゾール-5-イル) フェノキシ、2- (オキ
 10 サジアゾール-3-イル) フェノキシ、3- (オキサジアゾール-3-イル)
 フェノキシ、4- (オキサジアゾール-3-イル) フェノキシ、2- (5-メ
 チルオキサジアゾール-3-イル) フェノキシ、3- (5-メチルオキサジア
 ザール-3-イル) フェノキシ、4- (5-メチルオキサジアゾール-3-イ
 ル) フェノキシ、2-メトキシフェニルスルファニル、3-メトキシフェニル
 15 スルファニル、4-メトキシフェニルスルファニル、2-メトキシフェニルメ
 チルスルファニル、3-メトキシフェニルメチルスルファニル、4-メトキシ
 フェニルメチルスルファニル 2- (5-オキソ-4, 5-ジヒドロ- [1, 2,
 4] オキサジアゾール-3-イル) フェノキシ、3- (5-オキソ-4, 5-
 ジヒドロ- [1, 2, 4] オキサジアゾール-3-イル) フェノキシ、4-
 20 (5-オキソ-4, 5-ジヒドロ- [1, 2, 4] オキサジアゾール-3-イ
 ル) フェノキシ、2- (N-ヒドロキシアミジノ) フェノキシ、3- (N-ヒ
 ドロキシアミジノ) フェノキシ、4- (N-ヒドロキシアミジノ) フェノキシ、
 2'-フルオロビフェニル-4-イルオキシ、ピリジン-2-イルスルファニ
 ル、ピリジン-3-イルスルファニル、ピリジン-4-イルスルファニル、ピ
 25 リジン-4-イルスルホニルアミノピリジン-2-イルオキシ、ピリジン-
 2-イルオキシ、ピリジン-3-イルオキシ、ピリジン-4-イルオキシ、
 2-メトキシピリジン-3-イルオキシ、2-メトキシピリジン-4-イルオ
 キシ、6-メトキシピリジン-3-イルオキシ、6-メトキシピリジン-2-
 イルオキシ、3-メトキシピリジン-2-イルオキシ、4-メトキシピリジ

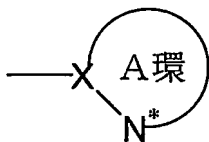
- ン-2-イルオキシ、5-メトキシピリジン-2-イルオキシ、6-メトキシ
メチルピリジン-3-イルオキシ、2-ジフルオロメトキシピリジン-3-イ
ルオキシ、4-ジフルオロメトキシピリジン-3-イルオキシ、6-メチルピ
リジン-2-イルスルファニル、5-メチルピリジン-2-イルスルファニル、
5 4-メチルピリジン-2-イルスルファニル、3-メチルピリジン-2-イル
スルファニル、4-シアノーピリジン-3-イルオキシ、6-シアノーピリジ
ン-3-イルオキシ、4-ジメチルカルバモイル-ピリジン-3-イルオキシ、
6-メタンスルホニル-ピリジン-3-イルオキシ、6-エタンスルホニル-
ピリジン-3-イルオキシ、4-メタンスルホニル-ピリジン-3-イルオキ
10 シ、2-シアノーピリジン-3-イルオキシ、2-ジメチルカルバモイル-ピ
リジン-3-イルオキシ、2-メタンスルホニル-ピリジン-3-イルオキシ、
2-メチルピリジン-3-イルスルファニル、2-クロロピリジン-3-イル
オキシ、6-アセチルアミノ-ピリジン-3-イルオキシ、2-オキソ-2
H-[1, 3']ピリジン-6'-イルオキシ、4-メチルピリジン-3-
15 イルスルファニル、5-メチルピリジン-3-イルスルファニル、6-メチル
ピリジン-3-イルスルファニル、2-メチルピリジン-4-イルスルファニ
ル、3-メチルピリジン-4-イルスルファニル、4-メチルピリジン-3-
イルスルホニル、5-メチルピリジン-3-イルスルホニル、6-メチルピリ
ジン-3-イルスルホニル、2-メチルピリジン-3-イルスルホニル、3-
20 メチルピリジン-2-イルスルホニル、4-メチルピリジン-2-イルスルホ
ニル、5-メチルピリジン-2-イルスルホニル、6-メチルピリジン-2-
イルスルホニル、2-オキソ-1, 2-ジヒドロピリジン-3-イルオキシ、
1-メチル-2-オキソ-1, 2-ジヒドロピリジン-3-イルオキシ、1-
エチル-2-オキソ-1, 2-ジヒドロピリジン-3-イルオキシ、5-プロ
25 モピリジン-2-イルオキシ、6-(5-メチル-[1, 2, 4]オキサジア
ゾール-3-イル-ピリジン)-3-イルオキシ、6-([1, 2, 4]オキ
サジアゾール-3-イル-ピリジン)-3-イルオキシ、1H-イミダゾ
ール-2-イルスルファニル、1-メチル-1H-イミダゾール-2-イルスル
ファニル、4H-[1, 2, 4]トリアゾール-3-イルスルファニル、4-

メチル-4H-[1, 2, 4] トリアゾール-3-イルスルファニル、6-
(2-メチル-2H-テトラゾール-5-イル) ピリジン-3-イルオキシ、
5- (2-オキソ-オキサジアゾリジン-3-イル) ピリジン-2-イルオキシ、
6-ピラジン-2-イル-ピリジン-3-イルオキシ、1-アセチルピロ
5 リジン-2-イル、2-アセチルピロリジン-1-イル、1-アセチル-3-
フルオロ-ピロリジン-2-イル、1-アセチル-5-メチル-ピロリジン-
2-イル、1-アセチルピペリジン-2-イル、1-エチルカルボニル-ピロ
リジン-2-イル、2-エチルカルボニルピロリジン-1-イル、1-エチル
カルボニル-ピペリジン-2-イル、1-n-プロピルカルボニル-ピロリジ
10 ン-2-イル、2-n-プロピルカルボニル-ピロリジン-2-イル、1-
n-プロピルカルボニル-ピペリジン-2-イル、1-イソプロピル-ピロリ
ジン-2-イル、2-イソプロピル-ピロリジン-1-イル、1-イソプロピ
ル-ピペリジン-2-イル、1-ヒドロキシエチルカルボニル-ピロリジン-
2-イル、2-ヒドロキシエチルカルボニル-ピロリジン-1-イル、1-ヒ
15 ドロキシエチルカルボニル-ピペリジン-2-イル、1-ヒドロキシメチルカ
ルボニル-ピロリジン-2-イル、2-ヒドロキシメチルカルボニル-ピロリ
ジン-1-イル、1-ヒドロキシメチルカルボニル-ピペリジン-2-イル、
1-メトキシメチルカルボニル-ピロリジン-2-イル、2-メトキシメチル
カルボニル-ピロリジン-1-イル、1-メトキシメチルカルボニル-ピペリ
20 ジン-2-イル、1-エトキシメチルカルボニル-ピロリジン-2-イル、
2-エトキシメチルカルボニル-ピロリジン-1-イル、1-エトキシメチル
カルボニル-ピペリジン-2-イル、1-メチルピロリジン-2-イル、2-
メチルピロリジン-1-イル、1-メチルピペリジン-2-イル、1-エチル
ピロリジン-2-イル、2-エチルピロリジン-1-イル、1-エチルピペリ
25 ジン-2-イル、1-フェニルカルボニル-ピロリジン-2-イル、2-フェ
ニルカルボニル-ピロリジン-1-イル、1-フェニルカルボニル-ピペリジ
ン-2-イル、1-フェネチルカルボニル-ピロリジン-2-イル、2-フェ
ネチルカルボニル-ピロリジン-1-イル、1-フェネチルカルボニル-ピペ
リジン-2-イル、1-ベンジルカルボニル-ピロリジン-2-イル、2-ベ

ンジルカルボニル-ピロリジン-1-イル、1-ベンジルカルボニル-ピペリジン-2-イル、1-ジメチルアミノメチルカルボニル-ピロリジン-2-イル、2-ジメチルアミノメチルカルボニル-ピロリジン-1-イル、1-ジメチルアミノメチルカルボニル-ピペリジン-2-イル、1-メチルアミノメチルカルボニル-ピロリジン-2-イル、2-メチルアミノメチルカルボニル-ピロリジン-1-イル、1-メチルアミノメチルカルボニル-ピペリジン-2-イル、1-シクロヘキシルカルボニル-ピロリジン-2-イル、2-シクロヘキシルカルボニル-ピロリジン-1-イル、1-シクロヘキシルカルボニル-ピペリジン-2-イル、1-シクロペンチルカルボニル-ピロリジン-2-イル、2-シクロペンチルカルボニル-ピロリジン-1-イル、1-シクロペンチルカルボニル-ピペリジン-2-イル、1-(1-メチル-3-オキソブチルカルボニル)-ピロリジン-2-イル、2-(1-メチル-3-オキソブチルカルボニル)-ピロリジン-1-イル、1-(1-メチル-3-オキソブチルカルボニル)-ピペリジン-2-イル、1-メタンスルホニル-ピロリジン-2-イル、2-メタンスルホニル-ピロリジン-1-イル、1-メタンスルホニル-ピペリジン-2-イル、1-エタンスルホニル-ピロリジン-2-イル、2-エタンスルホニル-ピロリジン-1-イル、1-エタンスルホニル-ピペリジン-2-イル、1-イソプロピルスルホニル-ピロリジン-2-イル、2-イソプロピルスルホニル-ピロリジン-1-イル、1-イソプロピルスルホニル-ピペリジン-2-イル、1-カルバモイル-ピロリジン-2-イル、2-カルバモイル-ピロリジン-1-イル、1-カルバモイル-ピペリジン-2-イル、1-カルバモイルメチル-ピロリジン-2-イル、2-カルバモイルメチル-ピロリジン-1-イル、1-カルバモイルメチル-ピペリジン-2-イル、1-カルバモイルエチル-ピロリジン-2-イル、2-カルバモイルエチル-ピロリジン-1-イル、1-カルバモイルエチル-ピペリジン-2-イル、1-(ピロリジン-2-イルカルボニル)ピロリジン-2-イル、2-(ピロリジン-2-イルカルボニル)ピロリジン-1-イル、1-(ピロリジン-2-イルカルボニル)-ピペリジン-2-イル、1-(ピリミジニル-2-イル)ピロリジン-2-イル、2-(ピリミジニル-2-イル)

- ピロリジン-1-イル、1-(ピリミジニル-2-イル) ピペリジン-2-イル、1-(ピラジニル-2-イル) ピロリジン-2-イル、2-(ピラジニル-2-イル) ピロリジン-1-イル、1-(ピラジニル-2-イル) ピペリジン-2-イル、1-(ピリジル-2-イル) ピロリジン-2-イル、2-
 5 (ピリジル-2-イル) ピロリジン-1-イル、1-(ピリジル-2-イル) ピペリジン-2-イル、1-(ピリジル-3-イル) ピロリジン-2-イル、2-(ピリジル-3-イル) ピロリジン-1-イル、1-(ピリジル-3-イル) ピペリジン-2-イル、1-トリフルオロメチルカルボニル-ピロリジン-2-イル、2-トリフルオロメチルカルボニル-ピロリジン-1-イル、
 10 1-トリフルオロメチルカルボニル-ピペリジン-2-イル、1-(2-ヒドロキシアセチル) ピロリジン-2-イル、2-(2-ヒドロキシアセチル) ピロリジン-1-イル、1-(2-ヒドロキシアセチル) ピペリジン-2-イル、1-(2-メチルアミノアセチル) ピロリジン-2-イル、2-(2-メチルアミノアセチル) ピロリジン-1-イル、1-(2-メチルアミノアセチル)
 15 ピペリジン-2-イル、1-(2-ジメチルアミノアセチル) ピロリジン-2-イル、2-(2-ジメチルアミノアセチル) ピロリジン-1-イル、1-(2-ジメチルアミノアセチル) ピペリジン-2-イル、1-n-プロピルアミノアセチル-ピロリジン-2-イル、2-n-プロピルアミノアセチル-ピロリジン-1-イル、1-n-プロピルアミノアセチル-ピペリジン-2-イル、
 20 1-イソプロピルアミノアセチル-ピロリジン-2-イル、2-イソプロピルアミノアセチル-ピロリジン-1-イル、1-イソプロピルアミノアセチル-ピペリジン-2-イル等が挙げられる。

A環は、式 (I I)



(II)

- 25 で表される窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を環内に1乃至3有していてもよい (式 I I 中のN*で表される窒素原子は

除く)、5乃至6員の含窒素芳香族複素環を示すか、或いは該5乃至6員の芳香族複素環とフェニル又はピリジルとが縮合した基を意味する。

Xは、炭素原子又は窒素原子を示す。

- 5 5乃至6員の含窒素芳香族複素環である場合のA環としては、より具体的には、例えば、チアゾリル、イミダゾリル、イソチアゾリル、チアジアゾリル、トリアゾリル、オキサゾリル、オキサジアゾリル、イソキサゾリル、ピラジニル、ピリジル、ピリダジニル、ピラゾリル、ピリミジニル等が挙げられ、これらのうち、チアゾリル、チアジアゾリル、イソキサゾリル、ピラジニル、ピリジル、ピリダジニル、トリアゾリル又はピラゾリルが好ましく、ピリジル、ピラジニル、チアゾリル、チアジアゾリル、
10 イソキサゾリル又はピラゾリルがより好ましい。

5乃至6員の含窒素芳香環とフェニル又はピリジルとが縮合した双環である場合のA環としては、より具体的には、例えば、インドリル、ベンゾイミダゾリル、ベンゾオキサゾリル、ピリドチアゾリル又はベンゾチアゾリルが挙げられる。

- 15 A環としては、5乃至6員の含窒素芳香族複素環が好ましい。

また、該A環は、前記記載の R^3 で示される置換基を該環内に1又は2有していてもよく、A環上の置換基が2存在する場合には、これらは同一又は異なっている。

- 20 R^3 としては、具体的には、例えば、メチル、エトキシ、ヒドロキシメチル、メトキシカルボニル、メトキシメチル、アミノメチル、シアノ、アセチル、フッ素、塩素、臭素又はジフルオロメチル等が挙げられる。

- 以上より、A環（該A環は、 R^3 で1乃至3置換されていてもよい）としては、より具体的には、例えば、3H-イミダゾール-4-イル、1H-イミダゾール-2-イル、[1, 2, 4]トリアゾール-3-イル、[1, 2, 3]トリアゾール-4-イル、ピラゾール-3-イル、ピラゾール-1-イル、ピリジン-2-イル、ピラジン-2-イル、オキサゾール-2-イル、オキサゾール-4-イル、[1, 2, 4]チアジアゾール-5-イル、[1, 2, 4]チアジアゾール-3-イル、チアゾール-2-イル、チアゾール-4-イル、
25 [1, 2, 5]チアジアゾール-3-イル、ピロール-2-イル、イソチア

ザール-3-イル、イソキサザール-3-イル、4-メチル-チアザール-
 2-イル、4-ヒドロキシメチル-チアザール-2-イル、4-メトキシカル
 ボニル-チアザール-2-イル、4-メトキシメチル-チアザール-2-イル、
 4-アミノメチル-チアザール-2-イル、4-シアノ-チアザール-2-イ
 5 ル、4-シアノ-チアザール-2-イル、4-フルオロ-チアザール-2-イ
 ル、イミダザール-2-イル、4-メチル-イミダザール-2-イル、4-メ
 トキシカルボニル-イミダザール-2-イル、イソチアザール-3-イル、
 4-ヒドロキシメチル-イソチアザール-3-イル、[1, 3, 4] チアジア
 ザール-2-イル、5-アセチル-[1, 3, 4] チアジアザール-2-イル、
 10 [1, 2, 4] トリアザール-2-イル、5-ヒドロキシメチル-[1, 2,
 4] トリアザール-3-イル、4-メチル-ピリジン-2-イル、4-メトキ
 シメチル-イミダザール-2-イル、4-アセチル-イミダザール-2-イル、
 5-ヒドロキシメチル-イミダザール-2-イル、5-メチル-[1, 3,
 4] チアジアザール-2-イル、5-フルオロ-[1, 3, 4] チアジアゾ
 15 ル-2-イル、5-メチル-[1, 2, 4] トリアザール-2-イル、5-ア
 セチル-[1, 2, 4] トリアザール-3-イル、4-メトキシメチル-イソ
 キサザール-2-イル、5-メチル-イソキサザール-3-イル、5-ヒドロ
 キシメチル-イソキサザール-3-イル、1-オキシ-ピラジン-2-イル、
 1-オキシ-ピリジン-2-イル、5-メトキシメチル-イソキサザール-
 20 3-イル、5-メチルカルボニル-イソキサザール-3-イル、5-クロロ-
 イソキサザール-3-イル、5-アミノメチル-イソキサザール-3-イル、
 4-メチル-1H-ピラザール-3-イル、ピリミジン-2-イル、ピリミジ
 ン-4-イル、ピリダジン-3-イル、6-メチル-ピリダジン-3-イル、
 2-メチル-チアザール-4-イル、チアゾロ[5, 4-b] ピリジン-2-
 25 イル、3-メチル-[1, 2, 4] チアジアゾリル-5-イル、1-メチル-
 1H-ピラザール-3-イル等が挙げられる。

R^2 は、ヒドロキシ、ホルミル、 $-\text{CH}_{3-a}\text{F}_a$ 、 $-\text{OCH}_{3-a}\text{F}_a$ 、アミノ、
 CN、ハロゲン、 C_{1-6} アルキル又は $-(\text{CH}_2)_{1-4}\text{OH}$ を意味する。

該 R^2 としては、ヒドロキシ、ホルミル、 $-\text{CH}_{3-a}\text{F}_a$ (好ましくはトリフル

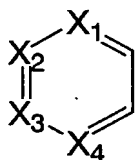
- オロメチル)、 $-\text{OCH}_{3-a}\text{F}_a$ 、ハロゲン、 C_{1-6} アルキル、アミノ、 CN^- 、 $-(\text{CH}_2)_{1-4}\text{OH}$ が好ましく、ヒドロキシ、ホルミル、 $-\text{CH}_{3-a}\text{F}_a$ (好ましくはトリフルオロメチル)、 $-\text{OCH}_{3-a}\text{F}_a$ (好ましくは、トリフルオロメトキシ)、アミノ、ハロゲン、 $-\text{C}_{1-6}$ アルキル、 CN 又は $-(\text{CH}_2)_{1-4}\text{OH}$ がより好ましく、ヒドロキシ、ホルミル、アミノ、ハロゲン (好ましくは、フルオロ及びクロロ)、 $-\text{C}_{1-6}$ アルキル又は $-(\text{CH}_2)_{1-4}\text{OH}$ がさらに好ましい。

q は、0乃至2の整数を示す。

q が2である場合には、 R^2 は同一又は異なってもよい。

- 10 ただし、式(I-0)で表される化合物のうち、 X_5 の一方が、酸素原子又は硫黄原子であり、 X_5 の他方が単結合であるか、或いは、 X_5 が共に単結合であり、かつ、 R^1 がアリール又は窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を環内に1乃至4有する4乃至10員の単環の若しくは双環の複素環 (該 R^1 は、それぞれ独立して、1乃至3の R^1 で置換されていてもよく、また、該複素環が、脂肪族複素環である場合には、二重結合を1又は2有していてもよい) である場合の化合物は、本発明に係る化合物から除かれる。

次に、前記式(I)中の部分構造である式(VII)



(VII)

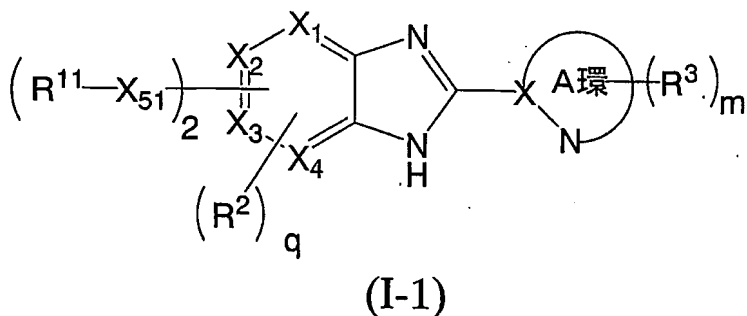
で表される基について説明する。

- 20 上記式(VII)中の X_1 乃至 X_4 は、炭素原子又は窒素原子であり、かつ、 X_1 乃至 X_4 のうち、少なくとも2つは、炭素原子を意味する。

上記式(VII)中の X_1 乃至 X_4 の全てが炭素原子である場合がより好ましい。

- また、本発明に係る化合物の好ましい態様としては、式(I-0)で表される化合物が、式(I-1)

25



〔式中、 R^{11} は、1乃至3の R^4 で置換されてもよいフェニル、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を環内に1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）を示し、かつ、 X_{51} が、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ を示し、他の記号は前記に同じ〕で表される場合が挙げられる。

R^{11} が示す「1乃至3の R^4 で置換されてもよいフェニル」とは、1乃至3の前記 R^4 で置換されていてもよいフェニルを示す。

10 R^{11} が示す「窒素原子、硫黄原子および酸素原子からなる群より選択されるヘテロ原子を環内に1乃至4有する5又は6員の含窒素芳香族複素環」とは、前記 R^1 の5又は6員の単環の芳香族複素環のうち、ヘテロ環構成原子として、少なくとも1つ環内に窒素原子を有する基を意味し、具体的には、例えば、ピロリル、ピラゾリル、イソキサゾリル、イソチアゾリル、イミダゾリル、オキサゾリル、チアゾリル、トリアゾリル、オキサジアゾリル、チアジアゾリル、

15 テトラゾリル、ピリジル、ピラジニル、ピリミジニル、ピリダジニル等が挙げられる。

式(I-1)中の X_1 、 X_2 、 X_3 及び X_4 は、前記式(I-0)と同様の基を意味し、 X_1 、 X_2 、 X_3 及び X_4 が全て炭素原子であることが好ましい。

20 式(I-1)中の R^4 は、前記式(I-0)中の R^4 と同様の基を意味する。

X_{51} は、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ を示し、これらのうち、 $-O-$ 又は $-S-$ が好ましく、 $-O-$ がより好ましい。

式(I-1)は、 $-X_{51}-R^{11}$ で表される基を2有するが、これらは同一又は異なってもよい。

式 (I-1) における $R^{11}-X_{51}-$ (R^{11} は、 R^4 で 1 乃至 3 置換されていてもよい) としては、具体的には、例えば、フェニルスルファニル、フェノキシ、ベンジルオキシ、2-シアノフェノキシ、3-シアノフェノキシ、4-シアノフェノキシ、2-カルバモイルフェノキシ、3-カルバモイルフェノキシ、
 5 4-カルバモイルフェノキシ、2-メチルカルバモイルフェノキシ、3-メチルカルバモイルフェノキシ、4-メチルカルバモイルフェノキシ、2-ジメチルカルバモイルフェノキシ、3-ジメチルカルバモイルフェノキシ、4-ジメチルカルバモイルフェノキシ、2-(ピロリジン-1-カルボニル)-フェノキシ、3-(ピロリジン-1-カルボニル)-フェノキシ、4-(ピロリジン-1-カルボニル)-フェノキシ、2-メトキシフェノキシ、3-メトキシフェノキシ、4-メトキシフェノキシ、2-イソプロピルフェノキシ、3-イソプロピルフェノキシ、4-イソプロピルフェノキシ、2-メチルフェノキシ、3-メチルフェノキシ、4-メチルフェノキシ、2-エチルフェノキシ、3-エチルフェノキシ、4-エチルフェノキシ、2-アセチルフェノキシ、
 15 3-アセチルフェノキシ、4-アセチルフェノキシ、2-メタンスルホニルフェノキシ、3-メタンスルホニルフェノキシ、4-メタンスルホニルフェノキシ、2-メトキシカルボニルフェノキシ、3-メトキシカルボニルフェノキシ、4-メトキシカルボニルフェノキシ、2-エトキシカルボニルフェノキシ、3-エトキシカルボニルフェノキシ、4-エトキシカルボニルフェノキシ、
 20 2-ヒドロキシフェノキシ、3-ヒドロキシフェノキシ、4-ヒドロキシフェノキシ、2-ヒドロキシメチルフェノキシ、3-ヒドロキシメチルフェノキシ、4-ヒドロキシメチルフェノキシ、2-ヒドロキシエチルフェノキシ、3-ヒドロキシエチルフェノキシ、4-ヒドロキシエチルフェノキシ、2-ホルミルフェノキシ、3-ホルミルフェノキシ、4-ホルミルフェノキシ、2-(1-ヒドロキシエチル)フェノキシ、3-(1-ヒドロキシエチル)フェノキシ、
 25 4-(1-ヒドロキシエチル)フェノキシ、2, 5-ジフルオロフェノキシ、2, 4-ジフルオロフェノキシ、2, 3-ジフルオロフェノキシ、2, 6-ジフルオロフェノキシ、2-フルオロフェノキシ、3-フルオロフェノキシ、4-フルオロフェノキシ、2-フルオロ-6-カルバモイルフェノキシ、2-

- ジーフルオロメトキシフェノキシ、3-ジフルオロメトキシフェノキシ、4-
 ジフルオロメトキシフェノキシ、2-トリフルオロメトキシフェノキシ、3-
 トリフルオロメトキシフェノキシ、4-トリフルオロメトキシフェノキシ、
 2-シアノー6-フルオロフェノキシ、2-(1H-テトラゾール-5-イ
 5 ル)フェノキシ、3-(1H-テトラゾール-5-イル)フェノキシ、4-
 (1H-テトラゾール-5-イル)フェノキシ、2-(オキサジアゾール-
 3-イル)フェノキシ、3-(オキサジアゾール-3-イル)フェノキシ、
 4-(オキサジアゾール-3-イル)フェノキシ、2-(5-メチルオキサジ
 アゾール-3-イル)フェノキシ、3-(5-メチルオキサジアゾール-3-
 10 イル)フェノキシ、4-(5-メチルオキサジアゾール-3-イル)フェノキ
 シ、2-メトキシフェニルスルファニル、3-メトキシフェニルスルファニル、
 4-メトキシフェニルスルファニル、2-メトキシフェニルメチルスルファニ
 ル、3-メトキシフェニルメチルスルファニル、4-メトキシフェニルメチル
 スルファニル、2-(5-オキソ-4,5-ジヒドロ-[1,2,4]オキサ
 15 ジアゾール-3-イル)フェノキシ、3-(5-オキソ-4,5-ジヒドロ-
 [1,2,4]オキサジアゾール-3-イル)フェノキシ、4-(5-オキ
 ソ-4,5-ジヒドロ-[1,2,4]オキサジアゾール-3-イル)フェノ
 キシ、2-(N-ヒドロキシアミジノ)フェノキシ、3-(N-ヒドロキシア
 ミジノ)フェノキシ、4-(N-ヒドロキシアミジノ)フェノキシ、ピリジ
 20 ン-2-イルスルファニル、ピリジン-3-イルスルファニル、ピリジン-
 4-イルスルファニル、ピリジン-2-イルオキシ、ピリジン-3-イルオキ
 シ、ピリジン-4-イルオキシ、2-メトキシピリジン-3-イルオキシ、
 2-メトキシピリジン-4-イルオキシ、6-メトキシピリジン-3-イルオ
 キシ、6-メトキシピリジン-2-イルオキシ、3-メトキシピリジン-2-
 25 イルオキシ、4-メトキシピリジン-2-イルオキシ、5-メトキシピリジ
 ン-2-イルオキシ、2-ジフルオロメトキシピリジン-3-イルオキシ、
 6-メチルピリジン-2-イルスルファニル、5-メチルピリジン-2-イル
 スルファニル、4-メチルピリジン-2-イルスルファニル、3-メチルピリ
 ジン-2-イルスルファニル、4-シアノーピリジン-3-イルオキシ、4-

ジメチルカルバモイルーピリジンー3-イルオキシ、4-メタンスルホニルー
 ピリジンー3-イルオキシ、2-シアノーピリジンー3-イルオキシ、2-ジ
 メチルカルバモイルーピリジンー3-イルオキシ、2-メタンスルホニルーピ
 リジンー3-イルオキシ、2-メチルピリジンー3-イルスルファニル、4-
 5 メチルピリジンー3-イルスルファニル、5-メチルピリジンー3-イルスル
 ファニル、6-メチルピリジンー3-イルスルファニル、2-メチルピリジ
 ンー4-イルスルファニル、3-メチルピリジンー4-イルスルファニル、
 4-メチルピリジンー3-イルスルホニル、5-メチルピリジンー3-イルス
 ルホニル、6-メチルピリジンー3-イルスルホニル、2-メチルピリジンー
 10 3-イルスルホニル、3-メチルピリジンー2-イルスルホニル、4-メチル
 ピリジンー2-イルスルホニル、5-メチルピリジンー2-イルスルホニル、
 6-メチルピリジンー2-イルスルホニル、2-オキソー1, 2-ジヒドロピ
 リジンー3-イルオキシ、1-メチルー2-オキソー1, 2-ジヒドロピリジ
 ンー3-イルオキシ、1-エチルー2-オキソー1, 2-ジヒドロピリジンー
 15 3-イルオキシ、1H-イミダゾールー2-イルスルファニル、1-メチルー
 1H-イミダゾールー2-イルスルファニル、4H-[1, 2, 4]トリア
 ザールー3-イルスルファニル又は4-メチルー4H-[1, 2, 4]トリア
 ザールー3-イルスルファニル等が挙げられる。

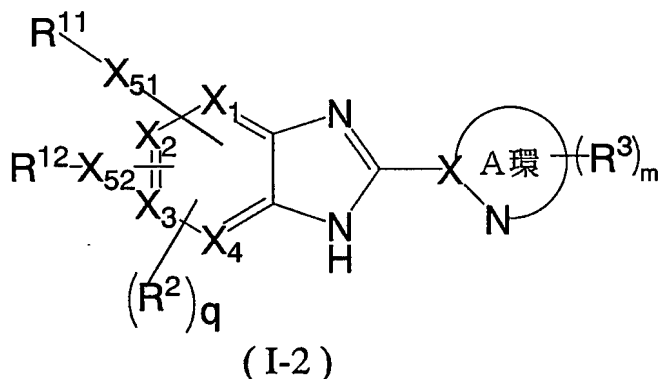
本発明に係る化合物の好ましい態様としては、前記式(I-1)中の R^{11} が
 20 共に、1乃至3の前記 R^4 で置換されていてもよい、フェニルである場合が挙げ
 られる。

また、本発明に係る化合物の好ましい態様としては、前記式(I-1)中の
 R^{11} が共に、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテ
 ロ原子を環内に1乃至4有する5又は6員の単環の含窒素芳香族複素環(該含
 25 窒素複素芳香環は、1乃至3の前記 R^4 で置換されていてもよい)である場合が
 挙げられる。

また、本発明に係る化合物の好ましい態様としては、前記式(I-1)中の
 R^{11} の一方が、1乃至3の前記 R^4 で置換されていてもよいフェニルであり、か
 つ、 R^{11} の他方が、窒素原子、硫黄原子及び酸素原子からなる群より選択され

るヘテロ原子を環内に1乃至4有する5又は6員の単環の含窒素芳香族複素環
(該含窒素芳香族複素環は、1乃至3の前記 R^4 で置換されていてもよい)であ
る場合が挙げられる。

また、本発明に係る化合物の好ましい態様としては、式(I-0)で表され
る化合物が、式(I-2)



[式中、 R^{12} は、複素環を構成する原子として、少なくとも窒素原子を1つ有
し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より
選択されるヘテロ原子を環内に1乃至4有していてもよい5乃至7員の含窒素
複素環(該 R^{12} は、1乃至3の前記 R^4 で置換されていてもよく、また、該 R^{12}
が脂肪族複素環である場合には、環内に二重結合を1又は2有していてもよ
い)を示し、 X_{52} は、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 又は単結
合であり、他の記号は前記に同じ]である場合が挙げられる。

R^{12} が示す「複素環を構成する原子として、少なくとも窒素原子を1つ有し、
他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選
択されるヘテロ原子を環内に1乃至4有していてもよい4乃至7員の含窒素複
素環」とは、前記 R^1 の4乃至7員の単環の複素環であって、かつ、複素環内に少
なくとも1つ窒素原子を有する基を意味し、具体的には、例えば、アゼチジ
ニル、ピロリジニル、ピペリジニル、アゼパニル、ピペラジニル、モルホリ
ノ、チオモルホリノ、ホモピペラジニル、イミダゾリジニル、ピラゾリジ
ニル、ピロリル、ピラゾリル、イソキサゾリル、イソチアゾリル、イミ
ダゾリル、オキサゾリル、チアゾリル、トリアゾリル、オキサジアゾリ
ル、チアジアゾリル、テトラゾリル、ピリジル、ピラジニル、ピリミジ
ニル又はピリダジニル等が挙

げられる。

R^{12} は、1乃至3の前記 R^4 を置換基として有していてもよい。

R^{12} が置換基として、 R^4 を2又は3有している場合には、これらは同一又は異なっているもよい。

- 5 R^{12} の置換基としては、前記 R^4 のうち、 $-C(O)-C_{1-6}$ アルキル（該 C_{1-6} アルキルは、ハロゲン、ヒドロキシ、 $-N(R^{51})R^{52}$ 、 $-O-C_{1-6}$ アルキル又はフェニルで置換されていてもよい）、 $-C(O)-$ フェニル、 $-C(O)-C_{3-7}$ シクロアルキル、 $-C(O)-O-C_{1-6}$ アルキル、 $-C(O)-N(R^{51})R^{52}$ 、 $-C_{1-6}$ アルキル、芳香族複素環、 $-S(O)_2-N$
10 $(R^{51})R^{52}$ 、 $-S(O)_2-C_{1-6}$ アルキルが好ましい。

- R^{12} の置換基としては、具体的には、例えば、アセチル、エチルカルボニル、プロピルカルボニル、イソプロピルカルボニル、ヒドロキシエチルカルボニル、ヒドロキシメチルカルボニル、メトキシメチルカルボニル、エトキシメチルカルボニル、メチル、エチル、フェニルカルボニル、フェネチルカルボニル、ペン
15 ジルカルボニル、ジメチルアミノメチルカルボニル、メチルアミノメチルカルボニル、シクロヘキシルカルボニル、シクロペンチルカルボニル、1-メチル-3-オキソブチルカルボニル、メタンスルホニル、エタンスルホニル、イソプロピルスルホニル、カルバモイル、カルバモイルメチル、カルバモイルエチル、ピロリジン-2-カルボニル、ピリジニル、ピラジニル、ピリジニル、
20 トリフルオロメチルカルボニル、2-ヒドロキシアセチル、2-メチルアミノアセチル、2-ジメチルアミノアセチル、2-エチルアミノアセチル、 n -プロピルアミノアセチル、イソプロピルアミノアセチル、オキソ、メチル、エチル、イソプロピル等が挙げられる。

- 式(I-2)中の X_{51} は、前記 X_{51} のうち、 $-O-$ 又は $-S-$ が好ましく、 $-O-$ がより好ましい。
25

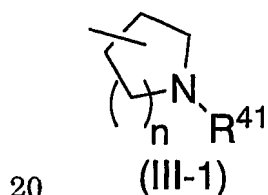
式(I-2)中の X_{52} は、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 又は単結合を示す。

R^{12} が、複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択さ

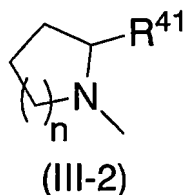
れるヘテロ原子を1乃至2有していてもよい4乃至7員の飽和の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1乃至3の前記 R^4 で置換されていてもよい）である場合には、 $X_{5,2}$ としては、単結合である場合が好ましい。

$R^{1,2}$ が、複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環（該5乃至7員の複素環は、1乃至3の前記 R^4 で置換されていてもよい）である場合には、 $X_{5,2}$ としては—O—、—S—、—S(O)—又は—S(O)₂—が好ましく、—O—がより好ましい。

$R^{1,2}$ が示す「複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよい4乃至7員の飽和の含窒素脂肪族複素環」としては、具体的には、例えば、アゼチジニル、ピロリジニル、ピペリジノ、ピペリジニル、ホモピペリジニル、アゼパニル、ピペラジニル、モルホリノ、チオモルホリノ、ホモピペラジニル、イミダゾリジニル、ピラゾリジニル等が挙げられ、これらのうち、アゼチジニル、ピロリジニル又はピペリジニルが好ましく、ピロリジニル、ピペリジニル、ホモピペリジニルが好ましく、式（III-1）

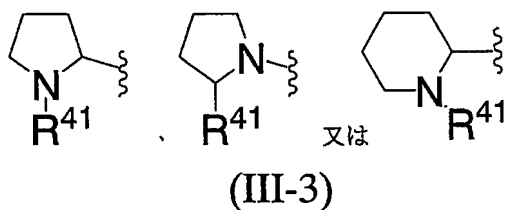


又は式（III-2）



〔式中、nは、1乃至3の整数を示し、 $R^{4,1}$ は、前記 R^4 と同じ〕で表される基

がより好ましく、式 (III-3)



[式中、 R^4 は前記定義と同様の基を示し、式 (VIII)]



(VIII)

5 は、 X_{53} との結合部位を示す]で表される基がさらに好ましい。

R^{12} が示す「複素環を構成する原子として、少なくとも窒素原子を1つ有し、かつ、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよい4乃至7員の飽和の含窒素脂肪族複素環(該含窒素脂肪族複素環は、1乃至3の前記 R^4 で置換されていて

10 もよい)」としては、具体的には、例えば、1-アセチルピロリジン-2-イル、2-アセチルピロリジン-1-イル、1-アセチル-3-フルオロピロリジン-2-イル、1-アセチル-5-メチルピロリジン-2-イル、1-アセチルピペリジン-2-イル、1-エチルカルボニル-ピロリジン-2-イル、2-エチルカルボニルピロリジン-1-イル、1-エチルカルボニル-ピペリジン-2-イル、1-n-プロピルカルボニル-ピロリジン-2-イル、2-n-プロピルカルボニル-ピロリジン-2-イル、1-n-プロピルカルボニル-ピペリジン-2-イル、1-イソプロピル-ピロリジン-2-イル、2-イソプロピル-ピロリジン-1-イル、1-イソプロピル-ピペリジン-2-イル、1-ヒドロキシエチルカルボニル-ピロリジン-2-イル、2-ヒドロキシエチルカルボニル-ピロリジン-1-イル、1-ヒドロキシエチルカルボニル-ピペリジン-2-イル、1-ヒドロキシメチルカルボニル-ピロリジン-2-イル、2-ヒドロキシメチルカルボニル-ピロリジン-1-イル、1-ヒドロキシメチルカルボニル-ピペリジン-2-イル、1-メトキシメチルカルボニル-ピロリジン-2-イル、2-メトキシメチルカルボニル-ピロ

15

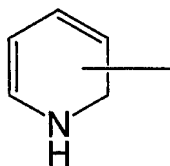
20

- リジン-1-イル、1-メトキシメチルカルボニル-ピペリジン-2-イル、
1-エトキシメチルカルボニル-ピロリジン-2-イル、2-エトキシメチル
カルボニル-ピロリジン-1-イル、1-エトキシメチルカルボニル-ピペリ
5 ジン-2-イル、1-メチルピロリジン-2-イル、2-メチルピロリジン-
1-イル、1-メチルピペリジン-2-イル、1-エチルピロリジン-2-イ
ル、2-エチルピロリジン-1-イル、1-エチルピペリジン-2-イル、
1-フェニルカルボニル-ピロリジン-2-イル、2-フェニルカルボニル-
ピロリジン-1-イル、1-フェニルカルボニル-ピペリジン-2-イル、
1-フェネチルカルボニル-ピロリジン-2-イル、2-フェネチルカルボニ
10 ル-ピロリジン-1-イル、1-フェネチルカルボニル-ピペリジン-2-イ
ル、1-ベンジルカルボニル-ピロリジン-2-イル、2-ベンジルカルボニ
ル-ピロリジン-1-イル、1-ベンジルカルボニル-ピペリジン-2-イル、
1-ジメチルアミノメチルカルボニル-ピロリジン-2-イル、2-ジメチル
アミノメチルカルボニル-ピロリジン-1-イル、1-ジメチルアミノメチル
15 カルボニル-ピペリジン-2-イル、1-メチルアミノメチルカルボニル-ピ
ロリジン-2-イル、2-メチルアミノメチルカルボニル-ピロリジン-1-
イル、1-メチルアミノメチルカルボニル-ピペリジン-2-イル、1-シク
ロヘキシルカルボニル-ピロリジン-2-イル、2-シクロヘキシルカルボニ
ル-ピロリジン-1-イル、1-シクロヘキシルカルボニル-ピペリジン-
20 2-イル、1-シクロペンチルカルボニル-ピロリジン-2-イル、2-シク
ロペンチルカルボニル-ピロリジン-1-イル、1-シクロペンチルカルボニ
ル-ピペリジン-2-イル、1-(1-メチル-3-オキソブチルカルボニ
ル)-ピロリジン-2-イル、2-(1-メチル-3-オキソブチルカルボニ
ル)-ピロリジン-1-イル、1-(1-メチル-3-オキソブチルカルボニ
25 ル)-ピペリジン-2-イル、1-メタンスルホニル-ピロリジン-2-イル、
2-メタンスルホニル-ピロリジン-1-イル、1-メタンスルホニル-ピペ
リジン-2-イル、1-エタンスルホニル-ピロリジン-2-イル、2-エタ
ンスルホニル-ピロリジン-1-イル、1-エタンスルホニル-ピペリジン-
2-イル、1-イソプロピルスルホニル-ピロリジン-2-イル、2-イソブ

- ロピルスルホニル-ピロリジン-1-イル、1-イソプロピルスルホニル-ピ
ペリジン-2-イル、1-カルバモイル-ピロリジン-2-イル、2-カルバ
モイル-ピロリジン-1-イル、1-カルバモイル-ピペリジン-2-イル、
1-カルバモイルメチル-ピロリジン-2-イル、2-カルバモイルメチル-
5 ピロリジン-1-イル、1-カルバモイルメチル-ピペリジン-2-イル、
1-カルバモイルエチル-ピロリジン-2-イル、2-カルバモイルエチル-
ピロリジン-1-イル、1-カルバモイルエチル-ピペリジン-2-イル、
1-(ピロリジン-2-イルカルボニル)ピロリジン-2-イル、2-(ピロ
リジン-2-イルカルボニル)ピロリジン-1-イル、1-(ピロリジン-
10 2-イルカルボニル)-ピペリジン-2-イル、1-(ピリミジニル-2-イ
ル)ピロリジン-2-イル、2-(ピリミジニル-2-イル)ピロリジン-
1-イル、1-(ピリミジニル-2-イル)ピペリジン-2-イル、1-(ピ
ラジニル-2-イル)ピロリジン-2-イル、2-(ピラジニル-2-イル)
ピロリジン-1-イル、1-(ピラジニル-2-イル)ピペリジン-2-イル、
15 1-(ピリジル-2-イル)ピロリジン-2-イル、2-(ピリジル-2-イ
ル)ピロリジン-1-イル、1-(ピリジル-2-イル)ピペリジン-2-イ
ル、1-(ピリジル-3-イル)ピロリジン-2-イル、2-(ピリジル-
3-イル)ピロリジン-1-イル、1-(ピリジル-3-イル)ピペリジン-
2-イル、1-トリフルオロメチルカルボニル-ピロリジン-2-イル、2-
20 トリフルオロメチルカルボニル-ピロリジン-1-イル、1-トリフルオロメ
チルカルボニル-ピペリジン-2-イル、1-(2-ヒドロキシアセチル)ピ
ロリジン-2-イル、2-(2-ヒドロキシアセチル)ピロリジン-1-イル、
1-(2-ヒドロキシアセチル)ピペリジン-2-イル、1-(2-メチルア
ミノアセチル)ピロリジン-2-イル、2-(2-メチルアミノアセチル)ピ
25 ロリジン-1-イル、1-(2-メチルアミノアセチル)ピペリジン-2-イ
ル、1-(2-ジメチルアミノアセチル)ピロリジン-2-イル、2-(2-
ジメチルアミノアセチル)ピロリジン-1-イル、1-(2-ジメチルアミノ
アセチル)ピペリジン-2-イル、1-n-プロピルアミノアセチル-ピロリ
ジン-2-イル、2-n-プロピルアミノアセチル-ピロリジン-1-イル、

1-n-プロピルアミノアセチル-ピペリジン-2-イル、1-イソプロピルアミノアセチル-ピロリジン-2-イル、2-イソプロピルアミノアセチル-ピロリジン-1-イル、1-イソプロピルアミノアセチル-ピペリジン-2-イル等が挙げられる。

- 5 R^{12} が示す「複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環」としては、具体的には、例えば、式 (IX)



10 (IX)

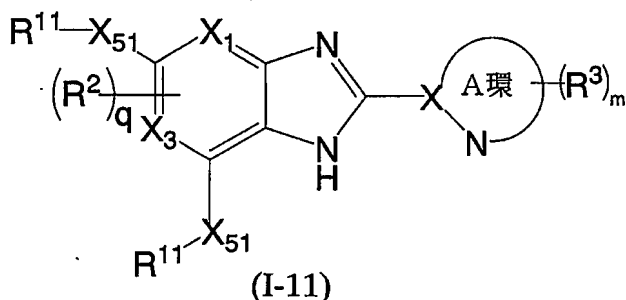
で表される基等が挙げられる。

- R^{12} が示す「複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環(該含窒素脂肪族複素環は、1乃至3の前記 R^4 で置換されていてもよい)」として、具体的には、例えば、1-メチル-2-オキソ-1, 2-ジヒドロピリジル、2-オキソ-1, 2-ジヒドロピリジル、1-エチル-2-オキソ-1, 2-ジヒドロピリジル、1-イソプロピル-2-オキソ-1, 2-ジヒドロピリジル、1-プロピル-2-オキソ-1, 2-ジヒドロピリジル等が挙げられる。
- 15 20

- また、式 (I-2) における $R^{11}-X_{51}-$ (R^{11} は、前記 R^4 で1乃至3置換されていてもよい) としては、前記式 (I-1) におけるものと同様の基が挙げられ、これらのうち、具体的には、例えば、5-ブロモピリジン-2-イルオキシ、6-メタンスルホニル-ピリジン-3-イルオキシ、2-クロロピリジン-3-イルオキシ、4-ヒドロキシメトキシメチル-フェノキシ、4-メタンスルホニルフェノキシ、6-エタンスルホニル-ピリジン-3-イルオ
- 25

キシ、6-シアノピリジン-3-イルオキシ、6-アセチルアミノ-ピリジン-3-イルオキシ、4-メトキシメチル-フェノキシ、4-(2-オキソ-2H-ピリジン-1-イル)フェノキシ、6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-イルオキシ、2'-フル
 5 オロビフェニル-4-イルオキシ、6-([1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-イルオキシ、6-(2-メチル-2H-テトラゾール-5-イル)-ピリジン-3-イルオキシ、4-(2-メチル-2H-テトラゾール-5-イル)フェノキシ、6-メトキシメチル-ピリジン-3-イルオキシ、2-オキソ-2H-[1, 3']ビピリジン-6'-イルオキシ、
 10 5-(2-オキソ-オキサゾリジノン-3-イル)ピリジン-2-イルオキシ、6-メチルピリジン-3-イルオキシ、6-ピラジン-2-イルピリジン-3-イルオキシ、4-アセチルフェノキシ等が好ましい。

本発明に係る化合物の好ましい態様としては、例えば、前記式(I-1)で表される化合物が、式(I-11)



[式中、各記号は前記に同じ] で表される場合が挙げられる。

式(I-11)中の R^{11} (該 R^{11} は、1乃至3の前記 R^4 で置換されていてもよい)は、前記式(I-1)中の R^{11} と同様の基が挙げられる。

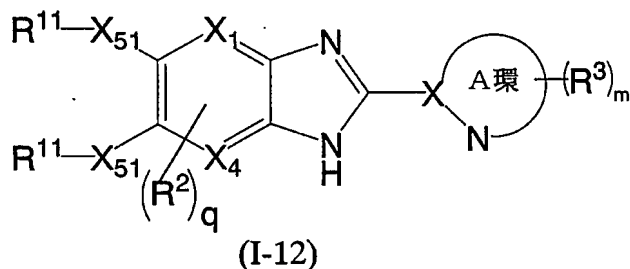
式(I-11)中の X_{51} としては、-O-又は-S-が好ましく、-O-が
 20 より好ましい。

式(I-11)中の X_1 及び X_3 は、それぞれ独立して、炭素原子又は窒素原子を示すが、 X_1 及び X_3 が共に、炭素原子である場合が好ましい。

式(I-11)における $R^{11}-X_{51}-$ (該 R^{11} は、1乃至3の前記 R^4 で置換されていてもよい)としては、具体的には、例えば、メタンスルホニルフェ

ノキシ、3-メタンスルホニルフェノキシ、2-メトキシフェノキシ、3-メ
トキシフェノキシ、2-アセチルフェノキシ、3-アセチルフェノキシ、2-
カルバモイルフェノキシ、3-カルバモイルフェノキシ、フェノキシ、2-シ
アノ-6-フルオロフェノキシ、2-メチルフェノキシ、3-メチルフェノキ
5 シ、2-フルオロフェノキシ、3-フルオロフェノキシ、2, 3-ジフルオロ
フェノキシ、2, 4-ジフルオロフェノキシ、2, 5-ジフルオロフェノキシ、
2, 6-ジフルオロフェノキシ、ピリジン-2-イルオキシ、ピリジン-3-
イルオキシ、2-メトキシピリジン-3-イルオキシ、2-ジフルオロメトキ
シピリジン-3-イルオキシ等が挙げられ、これらのうち、2-メタンスルホ
10 ニルフェノキシ、2-メトキシフェノキシ、2-アセチルフェノキシ、2-カ
ルバモイルフェノキシ、フェノキシ、2-シアノ-6-フルオロフェノキシ、
2-メチルフェノキシ、2-フルオロフェノキシ、2, 3-ジフルオロフェノ
キシ、2, 6-ジフルオロフェノキシ、ピリジン-3-イルオキシ、2-メト
キシピリジン-3-イルオキシ、2-ジフルオロメトキシピリジン-3-イル
15 オキシ等が好ましい。

また、本発明に係る化合物の好ましい態様としては、例えば、前記式 (I-
1) で表される化合物が、式 (I-12)



[式中、各記号は前記に同じ] で表される場合が挙げられる。

20 式 (I-12) 中の R^{11} (該 R^{11} は、1乃至3の前記 R^4 で置換されていても
よい) は、前記式 (I-1) 中の R^{11} と同様の基が挙げられる。

式 (I-12) 中の X_{51} としては、-O-又は-S-が好ましく、-O-が
より好ましい。

式 (I-12) 中の X_1 及び X_3 は、それぞれ独立して、炭素原子又は窒素原
25 子を示すが、 X_1 及び X_3 が共に、炭素原子である場合が好ましい。

式 (I-12) 中の $R^{11}-X_{51}-$ (該 R^{11} は、1乃至3の前記 R^4 で置換されていてもよい) としては、具体的には、例えば、2-カルバモイルフェノキシ、3-カルバモイルフェノキシ、4-カルバモイルフェノキシ、2-シアノフェノキシ、3-シアノフェノキシ、4-シアノフェノキシ、2-メトキシフェノキシ、3-メトキシフェノキシ、4-メトキシフェノキシ、2-メタンスルホニルフェノキシ、3-メタンスルホニルフェノキシ、4-メタンスルホニルフェノキシ、2-(ピロリジン-1-カルボニル)-フェノキシ、3-(ピロリジン-1-カルボニル)-フェノキシ、4-(ピロリジン-1-カルボニル)-フェノキシ、ピリジン-2-イルオキシ、ピリジン-3-イルオキシ、ピリジン-4-イルオキシ、2-メチルカルバモイルフェノキシ、3-メチルカルバモイルフェノキシ、4-メチルカルバモイルフェノキシ、2-ジメチルカルバモイルフェノキシ、3-ジメチルカルバモイルフェノキシ、4-ジメチルカルバモイルフェノキシ、2-(オキサジアゾール-3-イル)フェノキシ、2-メトキシカルボニルフェノキシ、3-メトキシカルボニルフェノキシ、4-メトキシカルボニルフェノキシ、2-アセチルフェノキシ、3-アセチルフェノキシ、4-アセチルフェノキシ、2-エトキシカルボニルフェノキシ、3-エトキシカルボニルフェノキシ、4-エトキシカルボニルフェノキシ、2-N-ヒドロキシアミジノ-フェノキシ、3-N-ヒドロキシアミジノ-フェノキシ、4-N-ヒドロキシアミジノ-フェノキシ、2-ヒドロキシメチル-フェノキシ、3-ヒドロキシメチル-フェノキシ、4-ヒドロキシメチル-フェノキシ、2-(2H-テトラゾール-5-イル)フェノキシ、3-(2H-テトラゾール-5-イル)フェノキシ、4-(2H-テトラゾール-5-イル)フェノキシ、2-シアノ-ピリジン-3-イルオキシ、4-シアノ-ピリジン-3-イルオキシ、2-カルバモイル-ピリジン-3-イル、2-ジフルオロメトキシ-ピリジン-3-イルオキシ、4-カルバモイル-ピリジン-3-イル、2-(5-オキソ-4,5-ジヒドロ-[1,2,4]オキサジアゾール-3-イル)フェノキシ、3-(5-オキソ-4,5-ジヒドロ-[1,2,4]オキサジアゾール-3-イル)フェノキシ、4-(5-オキソ-4,5-ジヒドロ-[1,2,4]オキサジアゾール-3-イル)フェノキシ、

ノキシ、2-ホルミルフェノキシ、3-ホルミルフェノキシ、4-ホルミルフェノキシ等が挙げられる。

これらのうち、例えば、 $R^{11}-X_{51}-$ の一方が、2-カルバモイルフェノキシ、4-カルバモイルフェノキシ、2-シアノフェノキシ、4-シアノフェノキシ、2-メトキシフェノキシ、4-メトキシフェノキシ、2-メタンスルホ
 5 ニルフェノキシ、4-メタンスルホニルフェノキシ、ピリジン-2-イルオキシ、ピリジン-3-イルオキシ、ピリジン-4-イルオキシ、2-シアノーピリジン-3-イルオキシ、2-ジフルオロメトキシ-ピリジン-3-イルオキシ、4-シアノーピリジン-3-イルオキシ、2-カルバモイル-ピリジン-
 10 3-イルオキシ、4-カルバモイル-ピリジン-3-イルオキシ、5-シアノーピリジン-3-イルオキシ、4-シアノーピリジン-3-イルオキシ、5-カルバモイル-ピリジン-3-イルオキシ、4-カルバモイル-ピリジン-3-イルオキシ、2-メチルカルバモイルフェノキシオキシ、4-メチルカルバモイルフェノキシオキシ、2-ジメチルカルバモイルフェノキシオキシ、
 15 4-ジメチルカルバモイルフェノキシ、2-(オキサジアゾール-3-イル)フェノキシ、2-メトキシカルボニルフェノキシ、4-メトキシカルボニルフェノキシ、2-アセチルフェノキシ、4-アセチルフェノキシ、2-エトキシカルボニルフェノキシ、4-エトキシカルボニルフェノキシ、2-N-ヒドロキシアミジノーフェノキシ、4-N-ヒドロキシアミジノーフェノキシ、
 20 2-ヒドロキシメチル-フェノキシ、4-ヒドロキシメチル-フェノキシ、2-ジフルオロメトキシ-ピリジン-3-イルオキシ、2-(2H-テトラゾール-5-イル)フェノキシ、4-(2H-テトラゾール-5-イル)フェノキシ、2-(5-オキソ-4, 5-ジヒドロ-[1, 2, 4]オキサジアゾール-3-イル)フェノキシ、4-(5-オキソ-4, 5-ジヒドロ-[1, 2, 4]オキサジアゾール-3-イル)フェノキシ、2-ホルミルフェノキシ、
 25 4-ホルミルフェノキシ等が好ましく、2-カルバモイルフェノキシ、2-シアノフェノキシ、2-メトキシフェノキシ、2-メタンスルホニルフェノキシ、ピリジン-3-イルオキシ、2-ジフルオロメトキシ-ピリジン-3-イルオキシ、2-メチルカルバモイルフェノキシ、2-ジメチルカルバモイルフェノ

- キシ、2-（オキサジアゾール-3-イル）フェノキシ、2-メトキシカルボ
 ニルフェノキシ、2-アセチルフェノキシ、2-エトキシカルボニルフェノキ
 シ、2-N-ヒドロキシアミジノ-フェノキシ、2-シアノ-ピリジン-3-
 イルオキシ、2-ジフルオロメトキシ-ピリジン-3-イルオキシ、2-カル
 5 バモイル-ピリジン-3-イルオキシ、2-ヒドロキシメチル-フェノキシ、
 2-（2H-テトラゾール-5-イル）フェノキシ、2-ジフルオロメトキ
 シ-ピリジン-3-イルオキシ、2-（5-オキソ-4, 5-ジヒドロ- [1,
 2, 4] オキサジアゾール-3-イル）フェノキシ、2-ホルミルフェノキシ
 等がより好ましい。
- 10 例えば、 $R^{11}-X_{51}$ -の他方が、3-カルバモイルフェノキシ、4-カルバ
 モイルフェノキシ、3-シアノフェノキシ、4-シアノフェノキシ、3-メト
 キシフェノキシ、4-メトキシフェノキシ、3-（ピロリジン-1-カルボニ
 ル）-フェノキシ、4-（ピロリジン-1-カルボニル）-フェノキシ、3-
 メタンスルホニルフェノキシ、4-メタンスルホニルフェノキシ、ピリジン-
 15 2-イルオキシ、ピリジン-3-イルオキシ、ピリジン-4-イルオキシ、
 2-ジフルオロメトキシ-ピリジン-3-イルオキシ、3-メチルカルバモイ
 ルフェノキシ、4-メチルカルバモイルフェノキシ、5-シアノ-ピリジン-
 3-イルオキシ、4-シアノ-ピリジン-3-イルオキシ、5-カルバモイ
 ル-ピリジン-3-イルオキシ、4-カルバモイル-ピリジン-3-イルオキ
 20 シ、3-ジメチルカルバモイルフェノキシ、4-ジメチルカルバモイルフェ
 ノキシ、4-（オキサジアゾール-3-イル）フェノキシ、3-メトキシカルボ
 ニルフェノキシ、4-メトキシカルボニルフェノキシ、3-アセチルフェノ
 キシ、4-アセチルフェノキシ、3-エトキシカルボニルフェノキシ、4-エト
 キシカルボニルフェノキシ、3-N-ヒドロキシアミジノ-フェノキシ、4-
 25 N-ヒドロキシアミジノ-フェノキシ、3-ヒドロキシメチル-フェノキシ、
 4-ヒドロキシメチル-フェノキシ、3-（2H-テトラゾール-5-イル）
 フェノキシ、4-（2H-テトラゾール-5-イル）フェノキシ、3-（5-
 オキソ-4, 5-ジヒドロ- [1, 2, 4] オキサジアゾール-3-イル）
 フェノキシ、4-（5-オキソ-4, 5-ジヒドロ- [1, 2, 4] オキサジ

アゾール-3-イル) フェノキシ、3-ホルミルフェノキシ、4-ホルミル
フェノキシ等が好ましく、4-カルバモイルフェノキシ、4-シアノフェノキ
シ、4-メトキシフェノキシ、4-メタンスルホニルフェノキシ、ピリジン-
3-イルオキシ、4-メチルカルバモイルフェノキシ、4-ジメチルカルバモ
5 イルフェノキシ、4-(オキサジアゾール-3-イル) フェノキシ、4-メト
キシカルボニルフェノキシ、4-アセチルフェノキシ、4-エトキシカルボニ
ルフェノキシ、4-N-ヒドロキシアミジノ-フェノキシ、4-ヒドロキシメ
チル-フェノキシ、4-シアノ-ピリジン-3-イルオキシ、2-ジフルオロ
メトキシ-ピリジン-3-イルオキシ、4-カルバモイル-ピリジン-3-イル
10 オキシ、4-(2H-テトラゾール-5-イル) フェノキシ、4-(5-オキ
ソー4, 5-ジヒドロ-[1, 2, 4] オキサジアゾール-3-イル) フェノ
キシ、4-ホルミルフェノキシ等がより好ましい。

また、本発明に係る化合物の好ましい態様としては、本発明に係る化合物が、
式(I-0)で表される化合物であって、 R^1 の一方が、1乃至3の R^4 で置換
15 されていてもよいフェニルであるか、或いは、窒素原子、硫黄原子及び酸素原
子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素
芳香族複素環(該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよ
い)であり、かつ、 R^1 の他方が、複素環を構成するヘテロ原子として、少なく
とも窒素原子を1つ有し、かつ、他のヘテロ原子として、窒素原子、硫黄原子
20 及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有していてもよ
い5乃至7員の含窒素複素環である場合が挙げられる。

該5乃至7員の含窒素複素環としては、5若しくは6員の含窒素芳香族複素
環又は5乃至7員の含窒素脂肪族複素環である場合が挙げられる。

5又は6員の含窒素芳香族複素環としては、具体的には、例えば、ピロリル、
25 フリル、チエニル、ピラゾリル、イソキサゾリル、イソチアゾリル、イミダゾ
リル、オキサゾリル、チアゾリル、トリアゾリル、オキサジアゾリル、チアジ
アゾリル、テトラゾリル、ピリジル、ピラジニル、ピリミジニル、ピリダジニ
ル等が挙げられる。

5乃至7員の含窒素脂肪族複素環としては、具体的には、例えば、アゼチジ

ニル、ピロリジニル、ピペリジノ、ピペリジニル、アゼパニル、ピペラジニル、モルホリノ、チオモルホリノ、ホモピペラジニル、イミダゾリジニル、ピラゾリジニル等が挙げられる。

該複素環は、1乃至3の前記 R^4 で置換されていてもよく、また、該複素環が、
5 脂肪族複素環である場合には、二重結合を1又は2有していてもよい。

また、本発明に係る化合物の好ましい態様としては、本発明に係る化合物が、式(I-0)で表される化合物であって、 R^1 の一方が、1乃至3の R^4 で置換されていてもよいフェニルであるか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）であり、かつ、 R^1 の他方が、複素環を構成するヘテロ原子として、少なくとも窒素原子を1つ有し、かつ、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有していてもよい5又は6員の含窒素複素芳香環である場合が挙げられる。

15 窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環としては、前記と同様の基が挙げられる。

また、本発明に係る化合物の好ましい態様としては、本発明に係る化合物が、式(I-0)で表される化合物であって、 R^1 の一方が、1乃至3の R^4 で置換
20 されていてもよいフェニルであるか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）であり、かつ、 R^1 の他方が、複素環を構成するヘテロ原子として、少なくとも窒素原子を1つ有し、かつ、他のヘテロ原子として、窒素原子、硫黄原子
25 及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよい5乃至7員の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1乃至3の R^4 で置換されていてもよく、また、環内に二重結合を1又は2有していてもよい）である場合が挙げられる。

式(I-0)で表される化合物のうち、好ましい化合物としては、具体的に

- は、例えば、5 - (4 - メタンスルホニル - フェノキシ) - 2 - ピラジン - 2 -
イル - 6 - (2 - カルバモイル - フェノキシ) - 1 H - ベンズイミダゾール、
5 - (2 - カルバモイル - フェノキシ) - 2 - ピリジン - 2 - イル - 6 -
(6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダ
5 ゾール、
5 - (2 - カルバモイル - フェノキシ) - 2 - ピラジン - 2 - イル - 6 -
(6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダ
ゾール、
5 - (2 - フルオロ - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (6 - メ
10 タンスルホニル - ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダゾール、
5 - (2 - ジフルオロメトキシ - ピリジン - 3 - イルオキシ) - 6 - (6 - メ
タンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1
H - ベンズイミダゾール、
5 - (2 - ジフルオロメトキシ - ピリジン - 3 - イルオキシ) - 6 - (6 - メ
15 タンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1
H - ベンズイミダゾール、
5 - (2 - ジフルオロメトキシ - ピリジン - 3 - イルオキシ) - 6 - (6 - メ
タンスルホニル - ピリジン - 3 - イルオキシ) - 2 - (1 - メチル - 1 H - ピ
ラゾール - 3 - イル) - 1 H - ベンズイミダゾール、
20 5 - (2 - シアノ - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (6 - エタ
ンスルホニル - ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダゾール、
5 - (2 - フルオロ - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (6 - エ
タンスルホニル - ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダゾール、
5 - (2 - フルオロ - フェノキシ) - 2 - (1 H - ピラゾール - 3 - イル) -
25 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 1 H - ベンズイ
ミダゾール、
5 - (2, 3 - ジフルオロ - フェノキシ) - 2 - (1 - メチル - 1 H - ピラ
ゾール - 3 - イル) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキ
シ) - 1 H - ベンズイミダゾール、

- 5 - (2, 4-ジフルオロ-フェノキシ) - 2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2, 5-ジフルオロ-フェノキシ) - 2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2, 6-ジフルオロ-フェノキシ) - 2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 10 5 - (2, 6-ジフルオロ-フェノキシ) - 2-(1-メチル-1H-ピラゾール-3-イル) - 6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2-フルオロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミ
- 15 ダゾール、
- 5 - (2-フルオロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 5 - (2-クロロピリジン-3-イルオキシ) - 6-(6-エタンスルホニル
- 20 ピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 5 - (2-クロロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 25 5 - (2-シアノピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール、

- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (6-エ
タンスルホニル-ピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1
H-ベンズイミダゾール、
- 5 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (6-エ
タンスルホニル-ピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1
H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (4-エ
タンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1 H-ベンズイミ
ダゾール、
- 10 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (4-エ
タンスルホニル-フェノキシ) - 2-ピラジン-2-イル-1 H-ベンズイミ
ダゾール、
- 5 - (2, 6-ジフルオロ-フェノキシ) - 2-ピリジン-2-イル-6 -
(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイミダ
15 ゾール、
- 5 - (2-カルバモイル-フェノキシ) - 2-ピリジン-2-イル-6 -
(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイミダ
ゾール、
- 5 - (2-フルオロ-6-シアノ-フェノキシ) - 2-ピリジン-2-イル-
20 6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイ
ミダゾール、
- 5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピリジン-2-
イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベ
ンズイミダゾール、
- 25 5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピラジン-2-
イル-6 - (4-エタンスルホニル-フェノキシ) - 1 H-ベンズイミダゾー
ル、

- 5 - (2-フルオロ-6-シアノ-フェノキシ) - 2-ピラジン-2-イル-
6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイ
ミダゾール、
- 5 - (2-フルオロ-6-(テトラゾール-5-イル)-フェノキシ) - 2-
5 ピラジン-2-イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキ
シ) - 1H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシピリジン-3-イルオキシ) - 6 - (3-クロ
ロ-4-メタンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1H-
ベンズイミダゾール、
- 10 4 - (2-フルオロ-フェノキシ) - 2 - (ピリジン-2-イル) - 6 -
(4-メタンスルホニル-フェノキシ) - 1H-ベンズイミダゾール、
4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-メタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダ
ゾール、
- 15 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-メタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダ
ゾール、
4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダ
20 ゾール、
4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダ
ゾール、
4 - (1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキ
25 シ) - 6 - (4-エタンスルホニル-フェノキシ) - 2-ピリジン-2-イ
ル-1H-ベンズイミダゾール、
4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2 - (1H-ピラゾール-3-イル) - 1H-ベ
ンズイミダゾール、

- 4 - (2 - フルオローフェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 4 - (2, 3 - ジフルオローフェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダ
- 5 ゾール、
- 4 - (2, 5 - ジフルオローフェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 4 - (2 - シアノ - 6 - フルオローフェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール
- 10 ミダゾール
- 4 - (2 - シアノ - 6 - フルオローフェノキシ) - 6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 15 4 - (2 - シアノ - 6 - フルオローフェノキシ) - 6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 1 - (2 - (6 - (5 - プロモ - ピリジン - 2 - イルオキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、
- 20 1 - (2 - (6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、
- 1 - (2 - (6 - (4 - ヒドロキシメチル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、
- 25 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、

2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イ
 ル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - カルボキサミ
 ド、

2 - ヒドロキシ - 1 - (2 - (6 - (4 - メタンスルホニル - 1 - フェノキ
 5 シ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピ
 ロリジン - 1 - イル) - エタノン、

1 - (2 - (6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) -
 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
 ン - 1 - イル) - エタノン、

10 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピラジン -
 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
 ル) - エタノン、

2 - フルオロ - 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) -
 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
 15 ン - 1 - イル) - エタノン、

5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 - イ
 ル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - ピリジン - 2 - カルボニ
 トリル、

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン -
 20 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
 ル) - 2 - メチルアミノ - エタノン、

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - (1 H - ピラ
 ザール - 3 - イル) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン -
 1 - イル) - エタノン、

25 1 - (4 - フルオロ - 2 - (6 - (4 - メタンスルホニル - フェノキシ) -
 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
 ン - 1 - イル) - エタノン、

N - (5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン -
 2 - イル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - ピリジン - 2 - イ

- ル) - アセタミド、
- 1 - (2 - (2 - (5 - プロモ - ピリジン - 2 - イル) - 6 - (4 - メタンスルホニル - フェノキシ) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、
- 5 N - (2 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - 2 - オキソ - エチル) - アセタミド、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (メトキシメチル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール・ートリフルオロ酢酸塩、
- 10 1 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) ピリジン - 2 (1 H) - オン、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 15 (2 - (2 - (5 - ((2' - フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 6 - イル) ピロリジン - 1 - イル) - 2 - オキソエチル) メチルアミン、
- 20 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - ([1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピラジン - 2 - イル - 1 H -
- 25 ベンズイミダゾール、
- 5 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 6 - (4 - (メタンスルホニル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (2 - メチル - 2

- H-テトラゾール-5-イル) ピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 6-(1-アセチルピロリジン-2-イル) -5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-
 5 ベンズイミダゾール、
- 5-(1-アセチル-5-メチルピロリジン-2-イル) -6-(4-(メタンスルホニル) フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 6-(1-アセチルピロリジン-2-イル) -5-(6-(2-メチル-2H-テトラゾール-5-イル) ピリジン-3-イル) オキシ) -2-ピラジン-2-イル-1H-ベンズイミダゾール、
 10 H-テトラゾール-5-イル) ピリジン-3-イル) オキシ) -2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 6-(1-アセチルピロリジン-2-イル) -5-(6-(メトキシメチルピロリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 15 2-(2-(5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル) ピロリジン-1-イル) -2-オキソエタノール、
- 2-(5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル) ピロリジン-1-カルボキサミド、
 20 5'-(6-(1-アセチルピロリジン-2-イル) -2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル) オキシ) -2H-1, 2'-ビピリジン-2-オン、
- 3-(4-(6-(1-アセチルピロリジン-2-イル) -2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル) オキシ) フェニル) -1, 3-オキサゾリジン-2-オン、
 25 6-(1-アセチルピロリジン-2-イル) -5-(6-メチルピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、

- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - ピラジン - 2 - イルピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 6 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 5 - ((2' - フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 3 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) - 1, 3 - オキサゾリジン - 2 - オン、
- 10 6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 5 - ((6 - ピラジン - 2 - イルピリジン - 3 - イル) オキシ) - 1 H - ベンズイミダゾール、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 15 1 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) エタノン、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) フェノキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 20 6 - (1 - アセチル - 5 - メチルピロリジン - 2 - イル) - 5 - (4 - メタン スルホニル - フェノキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 25 N - メチル - 2 - (2 - (5 - (4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 6 - イル) ピロリジン - 1 - イル) - 2 - オキソエタンアミン、
- 6 - (1 - アセチル - 5 - メチルピロリジン - 2 - イル) - 5 - ((6 - (メトキシメチル) ピリジン - 3 - イル) オキシ) - 2 - ピラジン - 2 - イル - 1

H-ベンズイミダゾール、

1- (1- (6- (4-メタンスルホニル-フェノキシ) -2-ピリジン-2-イル-3 H-ベンズイミダゾール-5-イル) -ピロリジン-2-イル) -エタノン、

- 5 1- (1- (6- (6-メタンスルホニル-ピリジン-3-イルオキシ) -2-ピリジン-2-イル-3 H-ベンズイミダゾール-5-イル) -ピロリジン-2-イル) -エタノン、

1- (1- (6- (6-エタンスルホニル-ピリジン-3-イルオキシ) -2-ピラジン-2-イル-3 H-ベンズイミダゾール-5-イル) -ピロリジン-2-イル) -エタノン若しくは

- 10 1- (1- (6- (6-エタンスルホニル-ピリジン-3-イルオキシ) -2-ピラジン-2-イル-3 H-ベンズイミダゾール-5-イル) -4-フルオロ-ピロリジン-2-イル) -エタノンである化合物又はその薬学的に許容される塩等が挙げられる。

- 15 本発明に係る新規2-ヘテロアリアル置換ベンズイミダゾール誘導体は、薬学的に許容される塩として存在することができる。当該塩としては、酸付加塩又は塩基付加塩を挙げることができる。

本発明に係る化合物は、その置換基の態様によって、光学異性体、ジアステレオ異性体、幾何異性体等の立体異性体又は互変異性体が存在する場合がある。

- 20 これらの異性体は、すべて本発明に係る化合物に包含されることは言うまでもない。更にこれらの異性体の任意の混合物も本発明に係る化合物に包含されることは言うまでもない。

本発明の化合物はグルコキナーゼ活性化作用を有することから、糖尿病の治療薬及び／又は予防薬として、さらには糖尿病の合併症の治療薬及び／又は予防薬として有用である。

- 25

ここで、糖尿病の合併症とは、糖尿病を発症することにより併発する疾病のことであり、当該糖尿病の合併症としては、例えば糖尿病性腎症、糖尿病性網膜症、糖尿病性神経症、糖尿病性動脈硬化症等が挙げられる。

本発明に係る化合物は、インスリン依存性糖尿病 (IDDM、insuli

ndependent diabetes mellitus) とインスリン非依存性糖尿病 (NIDDM、non-insulin dependent diabetes mellitus) のどちらのタイプの糖尿病にも適応可能である。

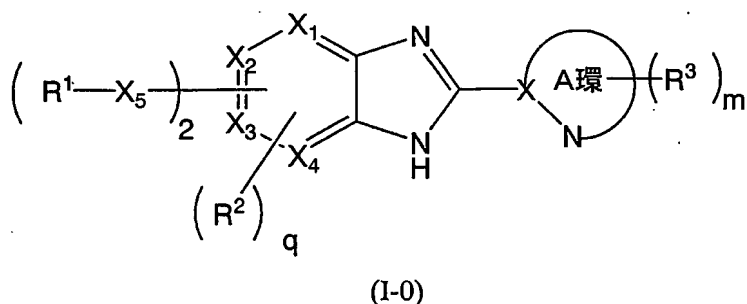
- 5 また、インスリン依存性糖尿病 (IDDM、insulin dependent diabetes mellitus) は、遺伝的なインスリン分泌低下と骨格筋でのインスリン抵抗性の素因に、肥満によるインスリン抵抗性が加わることにより発症に至り、おもに成人発症であると考えられている。

- 10 本発明に係る化合物は、I 型インスリン依存性糖尿病のみならず、従来の糖尿病薬では、十分な血糖値の低下を達成することが不可能であった II 型糖尿病についても、有用であると考えられる。

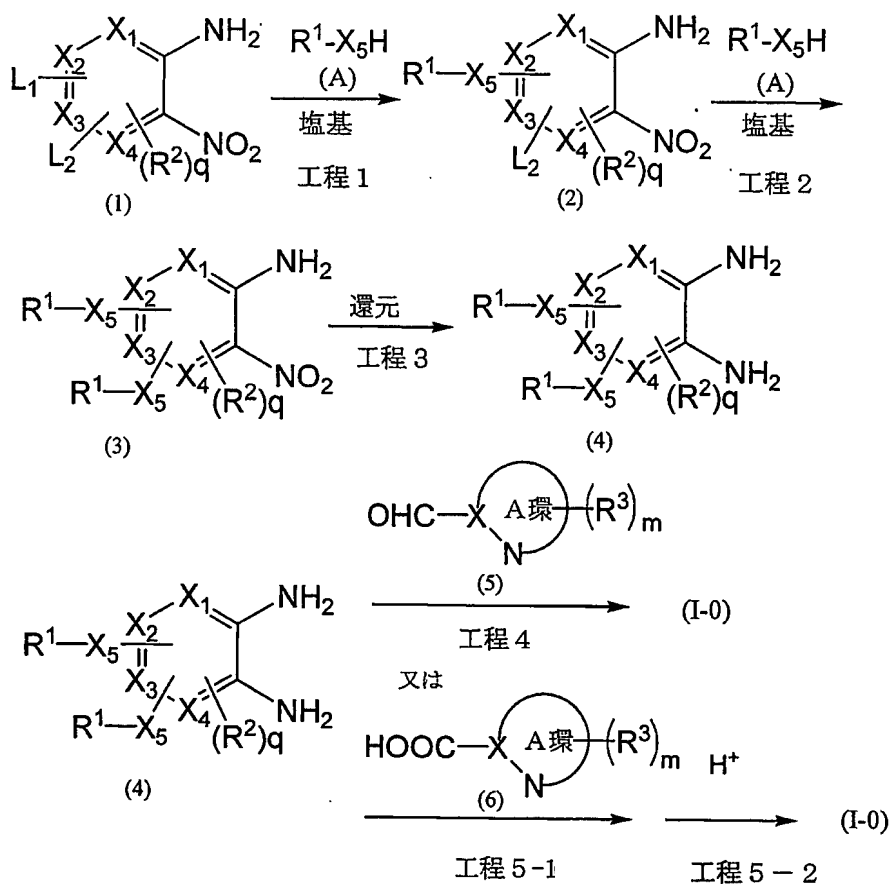
また、II 型糖尿病においては、摂食後高血糖の程度が健常人に比べて長時間持続することが顕著であるが、本発明に係る化合物又はその薬学的に許容される塩は、この II 型糖尿病に対しても有用である。

- 15 また、本発明に係る化合物又はその薬学的に許容される塩は、肥満症の治療及び／又は予防に有用である。

本発明に係る式 (I-0)



- 20 [式中、各記号は前記定義に同じ] で表される化合物は、例えば、以下の方法により製造することができる。



[式中、 L^1 及び L^2 は、ハロゲンなどの脱離基を示す。各記号は前記定義に同じ]

(工程 1) 本工程は、塩基の存在下、化合物 (1) と R^1-X_5H で表される化合物 (A) とを反応させて、化合物 (2) を製造する方法である。

L^1 及び L^2 としては、より具体的には、例えば、フッ素、塩素、臭素などのハロゲンが挙げられる。 L^1 及び L^2 は、同一又は異なってもよい。

本工程において用いられる化合物 (1) としては、例えば、3, 5-ジフルオロ-2-ニトロアニリン、3, 5-ジクロロ-2-ニトロアニリン、3, 5-ジブromo-2-ニトロアニリン、4-ブromo-5-フルオロ-2-ニトロアニリン、4, 5-ジフルオロ-2-ニトロアニリン等が挙げられる。

用いられる化合物 (A) の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物 (1) 1 当量に対して、通常 0.1 乃至 2.0 当量、好ましくは 0.5 乃至 5 当量である。

用いられる塩基の量は、用いられる化合物及び溶媒の種類その他の反応条件

により異なるが、通常0.1乃至20当量、好ましくは0.5乃至5当量である。

用いられる塩基としては、本工程において、化合物(1)と R^5-X_5H との反応において、化合物(2)を製造するものであれば、いかなるものを用いてもよいが、例えば、水素化ナトリウム、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム-tert-ブチラート、トリエチルアミン等が挙げられる。 R^5-X_5H が1級あるいは2級アミンの場合は、塩基を用いなくてもよい。

用いられる反応溶媒としては、不活性溶媒が挙げられ、反応に支障のない限り特に限定されないが、具体的には、例えば、ピリジン、トルエン、テトラヒドロフラン、1,4-ジオキサン、N,N-ジメチルホルムアミド、N,N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジン等が挙げられる。

本工程における反応温度は、通常0度乃至250度、好ましくは0度乃至150度である。

本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至5時間である。

このようにして得られる化合物(2)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程2)本工程は、塩基の存在下、前記工程1で得られた化合物(2)と前記工程1と同一又は異なる化合物(A)とを反応させて、化合物(3)を製造する方法である。

本工程は、前記工程1と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

(工程3)本工程は、前記工程2で得られた化合物(3)のニトロ基を還元して、化合物(4)を製造する方法である。

本工程において用いられる還元反応は、当業者に周知の方法が用いられる。本工程において用いられる還元反応としては、具体的には、例えば、水素、蟻

酸、蟻酸アンモニウム、ヒドラジン水和物とパラジウム、白金、ニッケル触媒を用いる接触還元法、塩酸、塩化アンモニウムと鉄を用いる還元法、メタノールと塩化スズを用いる還元法等が挙げられる。

上記還元反応において用いられる還元剤の量は、用いられる化合物及び溶媒
5 の種類その他の反応条件により異なるが、化合物（3）1当量に対して通常1乃至50当量、好ましくは2乃至20当量である。

用いられる反応溶媒としては、反応に支障のない限り、特に限定されないが、例えばメタノール、N，N-ジメチルホルムアミド、酢酸エチル、テトラヒドロフラン等及びこれらの混合溶媒を用いることができる。

10 反応温度及び反応時間は特に限定されないが、-10乃至100℃程度、好ましくは0乃至50℃程度の反応温度で1乃至20時間程度、好ましくは1乃至5時間程度反応を行う。

このようにして得られる化合物（4）は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離
15 精製するか又は単離精製することなく、次工程に付すことができる。

（工程4）本工程は、前記工程3で得られた化合物（4）と化合物（5）とを反応させることにより化合物（I）を製造する方法である。

本工程における環化反応は、文献記載の方法（例えば、シンセシス、2000年 第10巻、1380-1390頁、等）、それに準じた方法又はこれらと
20 常法とを組み合わせることにより行うことができる。

用いられる化合物（5）としては、例えば、ピリジンカルボキサルデヒド、ピラジンカルボキサルデヒド、1H-ピラゾール-3-カルボキサルデヒド等が挙げられる。

用いられる化合物（5）は、通常0.1乃至100当量、好ましくは0.1
25 乃至3当量である。

本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばニトロベンゼン、メタノール、テトラヒドロフラン、N，N-ジメチルホルムアミド、トルエン等又はそれら溶媒の混合物が挙げられる。

反応温度は、通常 0 度乃至反応溶媒の還流温度、好ましくは室温乃至反応溶媒の還流温度である。

反応時間は、通常 0.1 時間乃至 72 時間、好ましくは 0.1 時間乃至 24 時間である。

- 5 このようにして得られる本発明に係る化合物 (I) は、公知の分離精製手段、例えば濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製することができる。

(工程 5-1) 本工程は、前記工程 3 で得られた化合物 (4) と化合物 (6) とを反応させることにより縮合体を製造する方法である。

- 10 本工程におけるアミド反応は、化合物 (6) で表されるカルボン酸又はその反応性誘導体と、化合物 (4) を用いて行われる。

用いられる化合物 (6) 又はその反応性誘導体は、通常 0.1 乃至 100 当量、好ましくは 0.1 乃至 3 当量である。

- 15 化合物 (6) の「反応性誘導体」としては、例えば混合酸無水物、活性エステル、活性アミド等を挙げることができ、これらは例えば国際公開 WO 98/05641 号公報記載の方法によって得ることができる。

- 20 上記反応において、化合物 (6) で表されるカルボン酸を用いる場合には、例えばカルボニルジイミダゾール、N, N'-ジシクロヘキシルカルボジイミド、1-エチル-3-(3-ジメチルアミノプロピル)カルボジイミド、ジフェニルホスホリルアジド、ジピリジルジスルフィドートリフェニルホスフィン等、好ましくはカルボニルジイミダゾール等の縮合剤の存在下、反応を行うことが好ましい。

- 25 当該縮合剤の使用量は厳密に制限されるものではないが、通常、化合物 (6) に対して、通常 0.1 乃至 100 当量、好ましくは 0.1 乃至 10 当量である。

反応は、通常、不活性溶媒中で行われ、当該不活性溶媒としては、例えばテトラヒドロフラン、N, N-ジメチルホルムアミド、1, 4-ジオキサン、ベンゼン、トルエン、塩化メチレン、クロロホルム、四塩化炭素、1, 2-ジクロロエタン、ピリジン等、又はそれら溶媒の混合物が挙げられる。

反応温度は、通常 0 度乃至反応溶媒の還流温度、好ましくは室温乃至反応溶媒の還流温度である。

反応時間は、通常 0.1 時間乃至 72 時間、好ましくは 0.5 時間乃至 24 時間である。

- 5 また、上記反応は反応を円滑に進めるために塩基、縮合補助剤の存在下に行うことができる。

塩基としては、4-ジメチルアミノピリジン、トリエチルアミン等が挙げられる。

- 10 当該塩基の使用量は、化合物（6）で表されるカルボン酸又はその反応性誘導体 1 モルに対して、通常 0.1 乃至 100 当量、好ましくは 0.1 乃至 1 当量である。

縮合補助剤としては、N-ヒドロキシベンゾトリアゾール水和物、N-ヒドロキシスクシンイミド等が挙げられる。

- 15 当該縮合補助剤の使用量は、化合物（6）で表されるカルボン酸又はその反応性誘導体 1 モルに対して、通常 1 乃至 100 当量、好ましくは 1 乃至 5 当量である。

- 20 上記反応において、反応物質中に反応に関与しないアミノ基又はイミノ基が存在する場合、当該アミノ基又はイミノ基は、適宜、アミノ基又はイミノ基の保護基で保護した後に反応を行い、反応後に当該保護基を除去することが好ましい。

このようにして得られる縮合体は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

- 25 （工程 5-2）本工程は、前記工程 5-1 で得られた縮合体を環化反応させることにより化合物（I-0）を製造する方法である。

本工程における環化反応は、文献記載の方法（例えば、テトラヘドロン、2001 年 第 57 巻 9 号、1793-1800 頁に記載されている方法等）、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

環化反応に *p*-トルエンスルホン酸を用いる場合には、*p*-トルエンスルホン酸の量は、通常 0.1 乃至 100 当量、好ましくは 0.1 乃至 1 当量である。

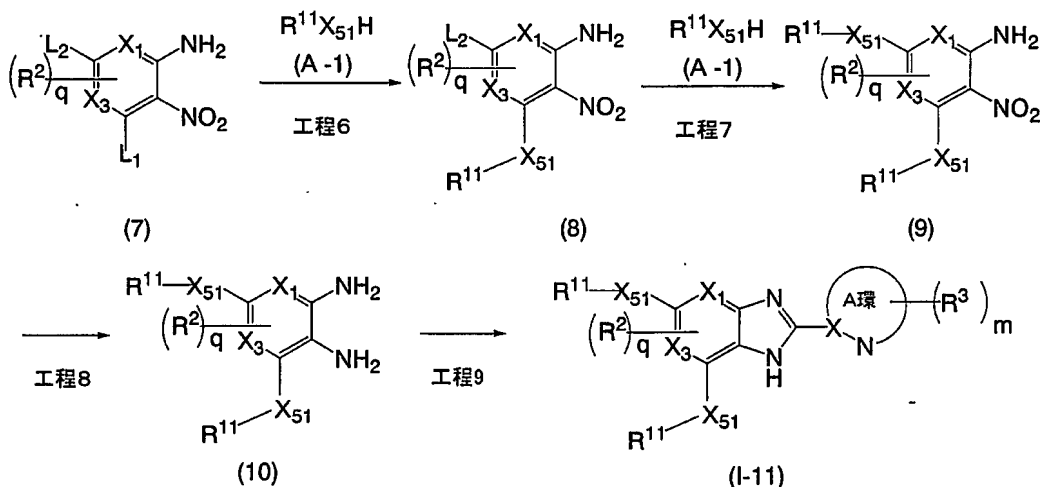
本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばトルエン、*N,N*-ジメチルホルムアミド、1,4-ジオキサン、*N*-メチルピロリジノン等又はそれら溶媒の混合物が挙げられる。

反応温度は、通常 0 度乃至 200 度、好ましくは室温乃至反応溶媒の還流温度である。

反応時間は、通常 0.1 時間乃至 72 時間、好ましくは 0.5 時間乃至 12 時間である。

このようにして得られる本発明に係る化合物 (I-0) は、公知の分離精製手段、例えば濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製することができる。

本発明に係る化合物 (I-11) は、以下の方法によっても製造することができる。



[式中、 L^1 、 L^2 は、ハロゲンなどの脱離基を示す。各記号は前記定義に同じ]

(工程 6) 本工程は、塩基の存在下、化合物 (7) と化合物 (A-1) とを反応させて、化合物 (8) を製造する方法である。

L^1 、 L^2 としては、より具体的には、例えば、フッ素、塩素、臭素などのハ

ロゲンが挙げられる。

用いられる化合物（A-1）の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物（7）1当量に対して、通常0.1乃至20当量、好ましくは0.5乃至5当量である。

- 5 用いられる塩基の量は、用いられる化合物及び溶媒の種類その他の反応条件により異なるが、通常0.1乃至20当量、好ましくは0.5乃至5当量である。

- 用いられる塩基としては、本工程において、化合物（7）と化合物（A-1）との反応において、化合物（8）を製造するものであれば、いかなるもの
10 を用いてもよいが、例えば、水素化ナトリウム、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム-tert-ブチラート、トリエチルアミン等が挙げられる。

- 用いられる反応溶媒としては、不活性溶媒が挙げられ、反応に支障のない限り特に限定されないが、具体的には、例えば、ピリジン、トルエン、テトラヒ
15 ドロフラン、1,4-ジオキサン、N,N-ジメチルホルムアミド、N,N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジノン等が挙げられる。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは0度乃至250度である。

- 20 本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.1時間乃至5時間である。

このようにして得られる化合物（8）は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離製精製することなく、次工程に付すことができる。

- 25 （工程7）本工程は、塩基の存在下、化合物（8）と前記工程1で用いた化合物（A-1）とを反応させて、化合物（9）を製造する方法である。

本工程は、前記工程6と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物（9）は、公知の分離精製手段、例えば、濃

縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付することができる。

(工程 8) 本工程は、化合物 (9) のニトロ基を還元して、化合物 (10) を製造する方法である。

- 5 本工程は、前記工程 3 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (10) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付することができる。

- 10 (工程 9) 本工程は、化合物 (10) と前記記載の化合物 (5) 又は化合物 (6) とを反応させることにより、本発明に係る化合物 (I-11) を製造する方法である。

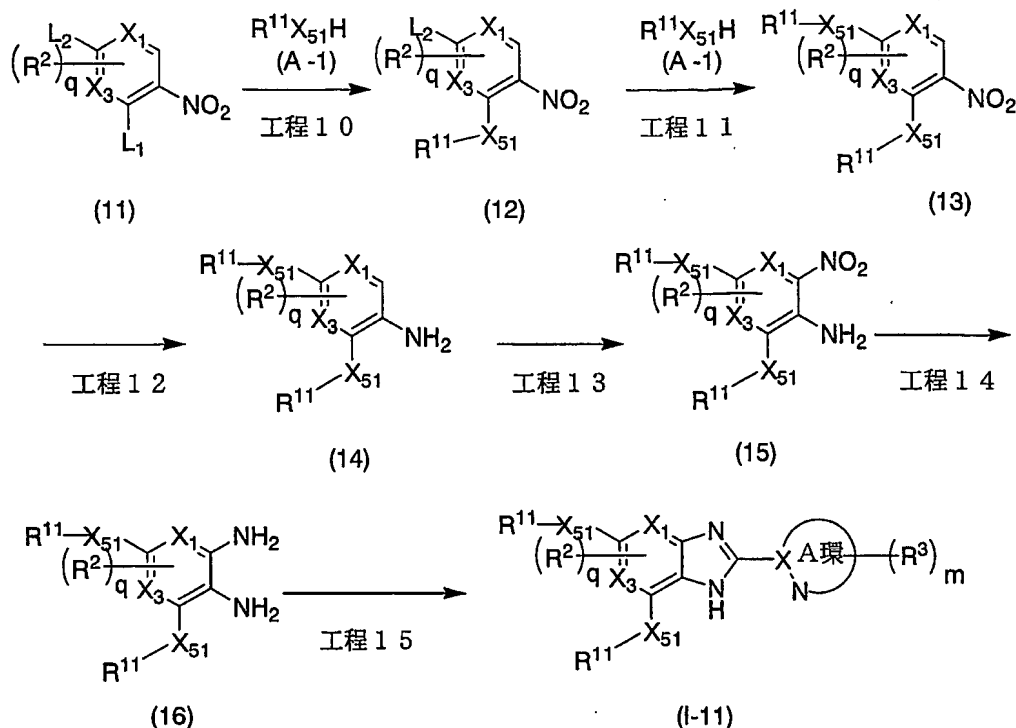
化合物 (10) と化合物 (5) との反応は、前記工程 4 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

- 15 また、化合物 (10) と化合物 (6) との反応は、前記工程 5-1 及び 5-2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる本発明に係る化合物 (I-11) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラ

- 20 フィー等により単離精製することができる。

本発明に係る化合物 (I-11) は、以下の方法によっても製造することができる。



[式中、 L^1 、 L^2 は、ハロゲンなどの脱離基を示す。各記号は前記定義に同じ]

(工程 1 0) 本工程は、化合物 (1 1) と前記記載の化合物 (A-1) とを反応させて、化合物 (1 2) を製造する方法である。

本工程は、前記工程 6 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (1 2) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 1 1) 本工程は、化合物 (1 2) と前記記載の化合物 (A-1) とを反応させて、化合物 (1 3) を製造する方法である。

本工程は、前記工程 6 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (1 3) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 1 2) 本工程は、化合物 (1 3) のニトロ基を還元して、化合物 (1 4) を製造する方法である。

本工程は、前記工程 3 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

- 5 このようにして得られる化合物 (1 4) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 1 3) 本工程は、前記工程で得られた化合物 (1 4) にニトロ基を導入して、化合物 (1 5) を製造する方法である。

- 10 本工程におけるニトロ化は、文献記載の方法 (例えばシンセティック コミュニケーション、2001年 第31巻7号、1123-1128頁、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。該ニトロ化反応は、必要に応じて、化合物 (1 4) の有するアミノ基を保護して行ってもよい。

- 15 ニトロ化に硝酸カリウムを用いる場合には、硝酸カリウムの量は、通常 0.1 乃至 100 当量、好ましくは 0.1 乃至 2 当量である。

本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばトリフルオロ酢酸、トリフルオロ酢酸無水物、塩酸、硫酸、硝酸等が挙げられる。

- 20 反応温度は、通常 0 度乃至反応溶媒の還流温度、好ましくは室温乃至 70 度である。

反応時間は、通常 0.1 時間乃至 72 時間、好ましくは 0.5 時間乃至 12 時間である。

- 25 このようにして得られる化合物 (1 5) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 1 4) 本工程は、化合物 (1 5) の有するニトロ基を還元して、化合物 (1 6) を製造する方法である。

本工程は、前記工程 3 と同様の方法、これに準じた方法又はこれらと常法と

を組み合わせることにより行うことができる。

このようにして得られる化合物(16)は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

- 5 (工程15)本工程は、化合物(16)と前記記載の化合物(5)又は化合物(6)とを反応させることにより、本発明に係る化合物(I-11)を製造する方法である。

化合物(16)と化合物(5)との反応は、前記工程4と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

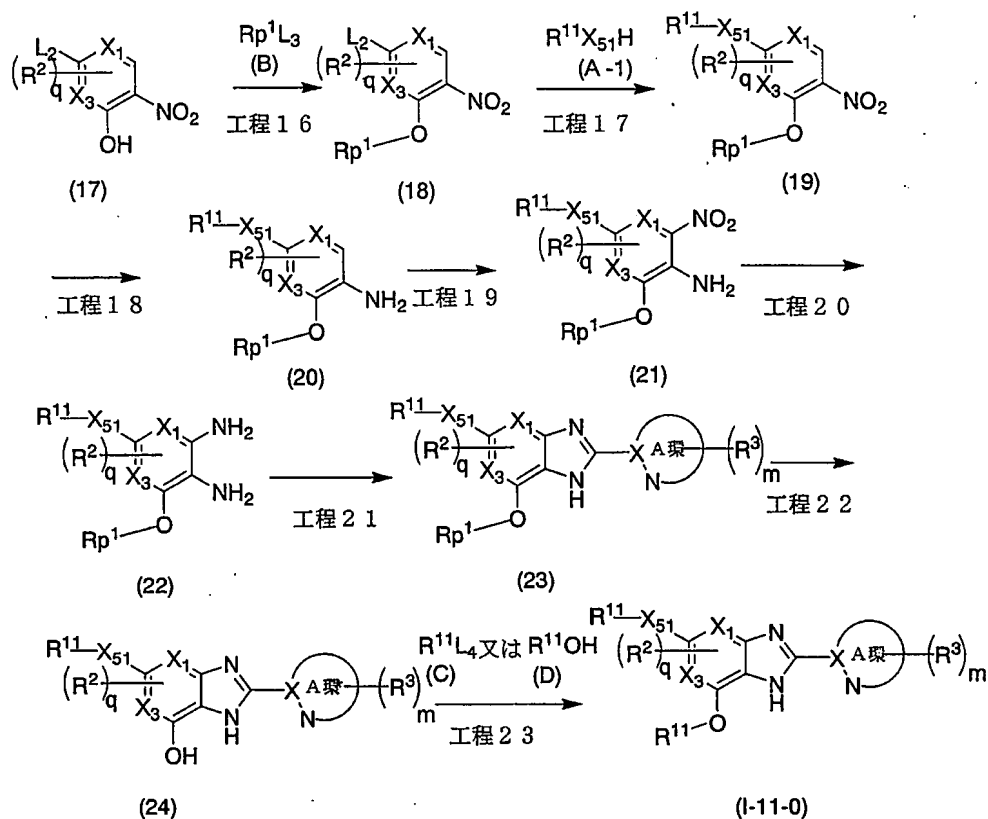
- 10 また、化合物(16)と化合物(6)との反応は、前記工程5-1及び5-2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

- また、上記化合物(14)と(6)とを反応させた後、ニトロ基を導入し、最後に該ニトロ基をアミノ基に還元すると同時に環化反応を行うか、或いは、
15 必要に応じて別途環化反応を行うことによっても、本発明に係る化合物(I-11)を製造することができる。

- なお、化合物(14)と化合物(6)とのアミド化、ニトロ化、ニトロ基からアミノ基への還元及び環化反応は、それぞれ、工程5-1、工程13、工程3及び工程5-1と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。
20

このようにして得られる本発明に係る化合物(I-11)は、公知の分離精製手段、例えば、濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製することができる。

- 本発明に係る化合物(I-11-0)は、例えば、以下の方法によっても製造
25 することができる。



[式中、 L^1 、 L^2 、 L^3 、 L^4 は、ハロゲンなどの脱離基を示す。 Rp^1 はヒドロキシの保護基を示す。各記号は前記定義に同じ]

- (工程 1 6) 本工程は、化合物 (1 7) に保護基を導入する反応である。本工程において用いられる化合物 (1 7) の有するヒドロキシの保護基 Rp^1 の導入は、前記記載の文献（例えばプロテクティブ グループス イン オーガニック シンセシス (Protective Groups in Organic Synthesis)、T. W. Green 著、第 2 版、John Wiley & Sons 社、1991 年、等）、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

Rp^1 としては、より具体的には、例えば、メトキシメチル、メチル、ベンジル、4-メトキシベンジル、2-(トリメチルシリル)エトキシメチル、2-(トリメチルシリル)エチル、tert-ブチルジメチルシリル、tert-ブチルカルボニル等が挙げられる。

- 用いられる化合物 (B) の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物 (1 7) 1 当量に対して、通常 0.1 乃至

20当量、好ましくは0.5乃至5当量である。

用いられる塩基の量は、用いられる化合物及び溶媒の種類その他の反応条件により異なるが、通常0.1乃至20当量、好ましくは0.5乃至5当量である。

- 5 用いられる塩基としては、本工程において、化合物(17)と化合物(B)との反応において、化合物(18)を製造するものであれば、いかなるものを用いてもよいが、例えば、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム-tert-ブチラート、トリエチルアミン、イミダゾール等が挙げられる。

- 10 反応温度は、通常0乃至反応溶媒の還流温度であり、好ましくは、0乃至80度である。

反応時間は、通常0.1時間乃至72時間であり、好ましくは、0.5乃至12時間である。

- 15 用いられる反応溶媒としては、不活性溶媒が挙げられ、反応に支障のない限り特に限定されないが、具体的には、例えば、ピリジン、トルエン、1,4-ジオキサン、N,N-ジメチルホルムアミド、N,N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジノン等が挙げられる。

- 20 このようにして得られる化合物(18)は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程17)本工程は、化合物(18)と前記化合物(A-1)とを反応させて、化合物(19)を製造する方法である。

本工程は、前記工程10と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

- 25 このようにして得られる化合物(19)は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程18)本工程は、化合物(19)の有するニトロ基を還元して、化合物(20)を製造する方法である。

本工程は、前記工程 1 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (2 0) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離
5 精製するか又は単離精製することなく、次工程に付すことができる。

(工程 1 9) 本工程は、化合物 (2 0) にニトロ基を導入して、化合物 (2 1) を製造する方法である。

本工程は、前記工程 1 3 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

10 このようにして得られる化合物 (2 1) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 2 0) 本工程は、化合物 (2 1) のニトロ基を還元して、化合物 (2 2) を製造する方法である。

15 本工程は、前記工程 1 4 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (2 2) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグフィーにより単離精製するか又は単離精製することなく、次工程に付すことができる。

20 (工程 2 1) 本工程は化合物 (2 2) と前記記載の化合物 (5) 又は化合物 (6) とを反応させることにより、化合物 (2 3) を製造する方法である。

化合物 (2 2) と化合物 (5) との反応は、前記工程 4 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

また、化合物 (2 2) と化合物 (6) との反応は、前記工程 5 - 1 及び 5 -
25 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (2 3) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 2 2) 本工程は、化合物 (2 3) のヒドロキシの保護基を除去して、化合物 (2 4) を製造する方法である。

本工程における保護基の除去は、文献記載の方法 (例えばプロテクティブグループスイン オーガニック シンセシス (Protective Groups in Organic Synthesis)、T. W. Green 著、第 2 版、John Wiley & Sons 社、1991 年、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができ、R^{p1} がベンジルの場合には、該保護基の除去は、例えば、パラジウム-炭素触媒等を用いる接触水素添加等を用いることにより行うことができる。

10 R^{p1} の除去に水酸化パラジウム-炭素触媒を用いる場合には、触媒の量は、通常 0.01 乃至 1000 当量、好ましくは 0.1 乃至 10 当量である。

本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばメタノール、エタノール等が挙げられる。

15 反応温度は、通常室温乃至反応溶媒の還流温度、好ましくは室温乃至 100 度である。

反応時間は、通常 0.1 時間乃至 72 時間、好ましくは 0.5 時間乃至 12 時間である。

このようにして得られる化合物 (2 4) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 2 3) 本工程は、化合物 (2 4) と化合物 (C) とを反応させる工程 (工程 2 3-1) か、又は化合物 (2 4) と化合物 (D) とを反応させる工程 (工程 2 3-2) により、本発明に係る化合物 (I-2) を製造する方法である。

25 (工程 2 3-1)

化合物 (C) 中の L₄ としては、具体的には、例えば、塩素、臭素、ヨウ素等のハロゲン原子が挙げられる。

用いられる化合物 (C) の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物 (2 4) 1 当量に対して、通常 0.1 乃至

20 当量、好ましくは0.5乃至5当量である。

本工程における反応は、塩基の存在下行われ、

用いられる塩基の量は、用いられる化合物及び溶媒の種類その他の反応条件により異なるが、化合物(24)1当量に対して、通常0.1乃至20当量、

5 好ましくは0.5乃至5当量である。

用いられる塩基としては、化合物(24)と化合物(C)との反応において、化合物(I-2)を製造するものであれば、いかなるものを用いてもよいが、例えば、水素化ナトリウム、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム-tert-ブチラート、トリエチル

10 ルアミン等が挙げられる。

用いられる反応溶媒としては、不活性溶媒が挙げられ、反応に支障のない限り特に限定されないが、具体的には、例えば、ピリジン、トルエン、テトラヒドロフラン、1,4-ジオキサン、N,N-ジメチルホルムアミド、N,N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジノ

15 ン等が挙げられる。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは0度乃至150度である。

本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至5時間である。

20 このようにして得られる本発明に係る化合物(I-2)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィ等により単離精製することができる。

(工程23-2)本工程は、前記工程で得られた化合物(24)と化合物(D)とを反応させ、必要に応じて、保護、脱保護を行うことにより本発明に

25 係る化合物(I-2)を製造する方法である。

化合物(24)と化合物(D)との反応は、いわゆる光延反応であり、ホスフィン化合物及びアゾ化合物の存在下、文献記載の方法(例えばミツノブ(Mitsunobu, O)著、「ユース オブ ジエチル アゾジカルボキシレート アンド トリフェニルホスフィン イン シンセシス アンド トラ

ンスフォーメーション オブ ナチュラル プロダクツ (The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products)」、シンセシス (Synthesis)、第1巻、1981年、p1-28)、それ

5 ンセシス (Synthesis)、第1巻、1981年、p1-28)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

本工程において用いられるアルコール化合物 (D) の量は、化合物 (24) 1当量に対して、通常0.5乃至10当量、好ましくは1乃至3当量である。

- 10 本工程において用いられるホスフィン化合物としては、通常例えばトリフェニルホスフィン、トリエチルホスフィン等が挙げられる。

用いられるホスフィン化合物の量は、化合物 (24) 1当量に対して、通常0.5乃至10当量であり、好ましくは1乃至3当量である。

- 15 用いられるアゾ化合物としては、例えばジエチルアゾジカルボキシレート、ジイソプロピルアゾジカルボキシレート等が挙げられる。

用いられるアゾ化合物の量は、化合物 (24) 1当量に対して、通常0.5乃至10当量、好ましくは1乃至3当量である。

本工程における反応時間は、通常1乃至48時間、好ましくは4乃至12時間である。

- 20 本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは15乃至30度である。

本工程において用いられる反応溶媒としては、反応に支障のないものであれば、特に限定されないが、具体的には、例えばテトラヒドロフラン、トルエン等が挙げられる。

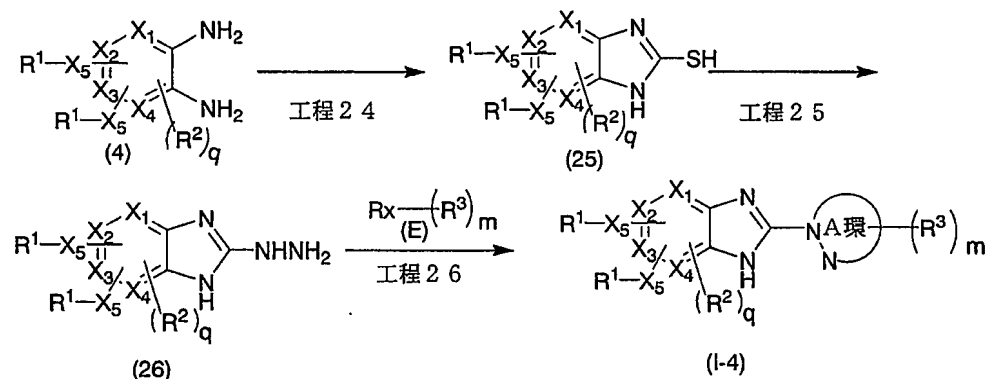
- 25 また、上記化合物 (20) と (6) とを反応させた後、ニトロ基を導入し、最後に該ニトロ基をアミノ基に還元すると同時に環化を行うか、或いは、必要に応じて別途環化反応を行うことによっても、本発明に係る化合物 (I-11-0) を製造することができる。

なお、化合物 (20) と化合物 (6) とのアミド化、ニトロ化、ニトロ基か

らアミノ基への還元及び環化反応は、それぞれ、工程 5-1、工程 13、工程 3 及び工程 5-1 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる本発明に係る化合物 (I-11-0) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製することができる。

本発明に係る化合物 (I) のうち、X が窒素原子である化合物 (I-4) は、以下の方法によっても製造することができる。



- 10 [式中、 R_x は、ハロゲン原子、アルデヒド、エステル、CN 又はそれらの等価体を 2 有する C_{1-6} アルキルを示し、他の記号は、前記と同じ]

(工程 24) 本工程は、化合物 (4) から化合物 (25) を製造する方法である。

- 15 この反応は、塩基性存在下、文献記載の方法 (例えば Indian J. Chem. Sect. B; 32; 2; 1993; 262-265.)、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

例えば二酸化硫黄を用いて反応を行う場合、用いる二酸化硫黄の量は、通常 0.1 乃至 500 当量、好ましくは 0.5 乃至 10 当量である。

- 20 用いられる塩基としては、化合物 (4) との反応において、化合物 (25) を製造するものであれば、いかなるものを用いてもよいが、例えば、水酸化ナトリウム、水素化ナトリウム、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム-tert-ブチラート、トリエチルアミン等が挙げられる。

本工程における反応時間は、通常1乃至48時間、好ましくは4乃至12時間である。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは0乃至溶媒の還流温度である。

- 5 本工程において用いられる反応溶媒としては、反応に支障のないものであれば、特に限定されないが、具体的には、例えばエタノール、水、トルエン、テトラヒドロフラン、1, 4-ジオキサン、N, N-ジメチルホルムアミド、N, N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジノン等が挙げられる。
- 10 このようにして得られる化合物(25)は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

- (工程25) 本工程は、化合物(25)を用いて、化合物(26)を製造する工程である。本工程における反応は、ヒドラジン-水和物を用いて、文献
- 15 記載の方法(例えば、Indian J. Chem. Sect. B; EN; 32; 2; 1993; 262-265.)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

用いるヒドラジン-水和物の量は、通常0.1乃至1000当量、好ましくは1乃至100当量である。

- 20 本工程における反応時間は、通常1乃至48時間、好ましくは4乃至24時間である。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは0乃至溶媒の還流温度である。

- 本工程における反応は、無溶媒で行うことが好ましいが、反応に支障のない
- 25 ものであれば、反応溶媒を用いてもよく、用いられる反応溶媒としては、具体的には、例えばエタノール、水、トルエン、テトラヒドロフラン、1, 4-ジオキサン、N, N-ジメチルホルムアミド、N, N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジノン等が挙げられる。

このようにして得られる化合物(26)は、公知の分離精製手段、例えば、

濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付することができる。

(工程 26) 本工程は、化合物 (26) と化合物 (E) とを反応させることにより、本発明に係る化合物 (I-4) を製造する方法である。

- 5 本工程における反応は、文献記載の方法 (例えば Indian J. Chem. Sect. B; EN; 32; 2; 1993; 262-265、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

10 例えばピラゾールを構築する場合、テトラメトキシプロパンを用いて反応を行うことにより合成することができる。

用いられるテトラメトキシプロパンの量は、通常 0.1 乃至 500 当量、好ましくは 0.5 乃至 100 当量である。

本工程における反応時間は、通常 1 乃至 48 時間、好ましくは 4 乃至 12 時間である。

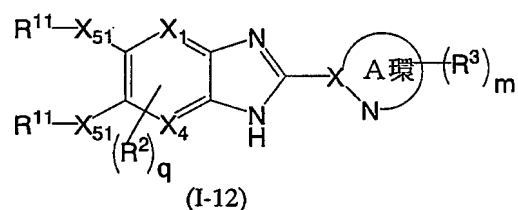
- 15 本工程における反応温度は、通常 0 度乃至反応溶媒の還流温度、好ましくは 0 乃至溶媒の還流温度である。

本工程において用いられる反応溶媒としては、反応に支障のないものであれば、特に限定されないが、具体的には、例えばエタノール、水、トルエン、テトラヒドロフラン、1,4-ジオキサン、N,N-ジメチルホルムアミド、N,N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジノン等が挙げられる。

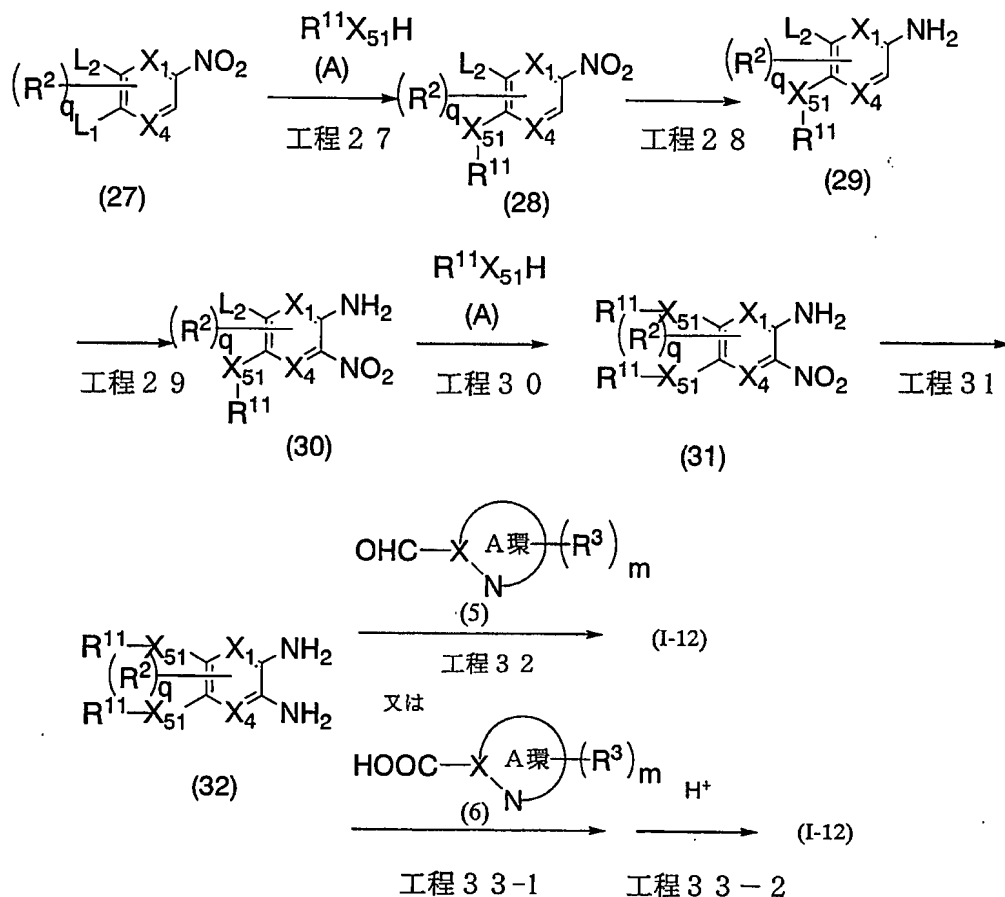
20

このようにして得られる本発明に係る化合物 (I-4) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製することができる。

- 25 本発明に係る化合物 (I-12)



〔式中、各記号は前記と同じ〕で表される化合物は、例えば、以下の方法によっても製造することができる。



- 5 〔式中、 L^1 、 L^2 は、ハロゲンなどの脱離基を示し、他の記号は、前記と同じ〕

（工程 2 7）本工程は、塩基の存在下、化合物（2 7）と前記化合物（A-1）とを反応させて、化合物（2 8）を製造する方法である。

- 10 L^1 、 L^2 としては、より具体的には、例えば、フッ素、塩素、臭素などのハロゲンが挙げられる。

用いられる化合物（A-1）の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物（2 7）1 当量に対して、通常 0.1 乃至 2.0 当量、好ましくは 0.5 乃至 5 当量である。

用いられる塩基の量は、用いられる化合物及び溶媒の種類その他の反応条件

により異なるが、通常0.1乃至20当量、好ましくは0.5乃至5当量である。

用いられる塩基としては、本工程において、化合物(27)と化合物(A-1)との反応において、化合物(28)を製造するものであれば、いかなるものを用いてもよいが、例えば、水素化ナトリウム、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム-tert-ブチラート、トリエチルアミン等が挙げられる。

用いられる反応溶媒としては、不活性溶媒が挙げられ、反応に支障のない限り特に限定されないが、具体的には、例えば、ピリジン、トルエン、テトラヒドロフラン、1,4-ジオキサン、N,N-ジメチルホルムアミド、N,N-ジメチルアセトアミド、ジメチルスルホキシド、1-メチル-2-ピロリジノン等が挙げられる。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは室温乃至150度である。

15 本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至5時間である。

このようにして得られる化合物(28)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離製精製することなく、次工程に付すことができる。

20 (工程28)本工程は、前記工程で得られた化合物(28)のニトロ基を還元して、化合物(29)を製造する方法である。

本工程において用いられる還元反応は、当業者に周知の方法が用いられる。本工程において用いられる還元反応としては、具体的には、例えば、水素、蟻酸、蟻酸アンモニウム、ヒドラジン水和物とパラジウム、白金、ニッケル触媒を用いる接触還元法、塩酸、塩化アンモニウムと鉄を用いる還元法、メタノールと塩化スズを用いる還元法等が挙げられる。

本工程において、ニトロ基の還元10%パラジウム-炭素触媒を用いる場合には、10%パラジウム-炭素触媒の量は、通常0.01乃至10当量、好ましくは0.1乃至1当量である。

本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばメタノール、エタノール、テトラヒドロフラン、N、N-ジメチルホルムアミド等が挙げられる。

5 反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは室温乃至反応溶媒の還流温度である。

反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至12時間である。

このようにして得られる化合物(29)は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単
10 離精製するか又は単離精製することなく、次工程に付すことができる。

(工程29)本工程は、前記工程で得られた化合物(29)にニトロ基を導入して、化合物(30)を製造する方法である。

本工程におけるニトロ化は、必要に応じて、アニリンに保護基をつけた後、文献記載の方法(例えばシンセティック コミュニケーション(Synthetic
15 ic Communication)、2001年 第31巻7号、1123-1128頁、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

ニトロ化に硝酸カリウムを用いる場合には、硝酸カリウムの量は、通常0.1乃至100当量、好ましくは0.1乃至1当量である。

20 本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばトリフルオロ酢酸、トリフルオロ酢酸無水物、塩酸、硫酸、硝酸等が挙げられる。

反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは室温乃至反応溶媒の還流温度である。

25 反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至12時間である。

このようにして得られる化合物(30)は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 3 0) 本工程は、前記工程で得られた化合物 (3 0) と前記化合物 (A-1) とを反応させることにより化合物 (3 1) を製造する方法である。

本工程は、必要に応じて、アニリンに保護基をつけた後、前記工程 2 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (3 1) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 3 1) 本工程は、前記工程 3 0 で得られた化合物 (3 1) のニトロ基を還元して、化合物 (3 2) を製造する方法である。

本工程における反応は、前記工程 8 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (3 2) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 3 2) 本工程は、前記工程 3 1 で得られた化合物 (3 2) と化合物 (5) とを反応させることにより本発明に係る化合物 (I-2) を製造する方法である。

本工程における反応は、前記工程 4 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる本発明に係る化合物 (I-2) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製することができる。

(工程 3 3-1) 本工程は、前記工程 3 1 で得られた化合物 (3 2) と化合物 (6) とを反応させることにより縮合体を製造する方法である。

本工程における反応は、前記工程 5-1 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる縮合体は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグフィー等により単離精製するか

前記工程 27 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (34) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単
5 離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 35) 本工程は、化合物 (34) と前記化合物 (A-1) とを反応させることにより、化合物 (35) を製造する方法である。本工程における反応は、前記工程 30 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

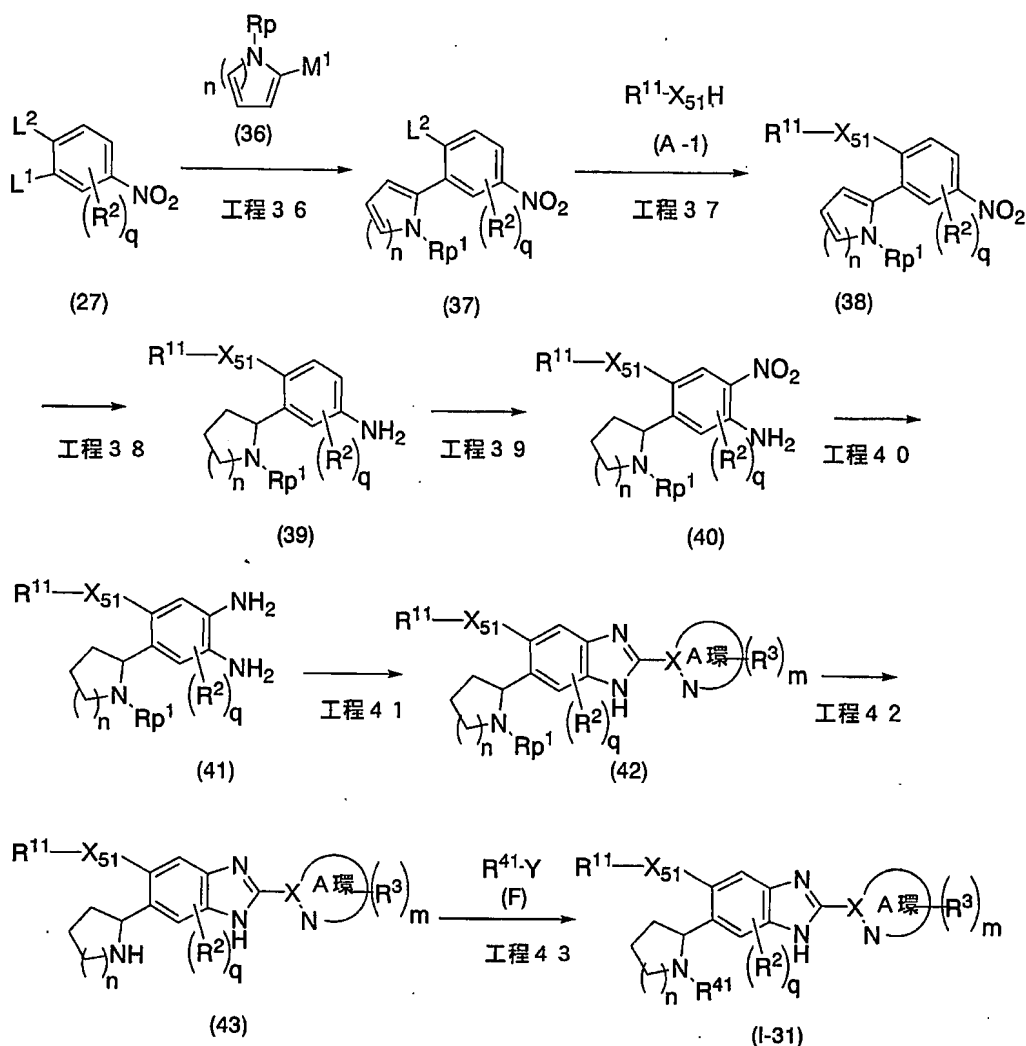
10 このようにして得られる化合物 (35) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 33-1) 本工程は、前記工程 35 で得られた化合物 (35) の有する -C(O)OR⁸ をアミノ基に変換して、化合物 (31) を製造する方法であり、例えば、いわゆるクルチウス (Curtius) 転移反応が挙げられる。
15 本工程における反応は、後述の工程 48 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (31) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精
20 製することができる。

得られた化合物 (31) を用いて、前記工程 31、32、33-1 又は 33-2 の方法を用いて、本発明に係る化合物 (I-12) を製造することができる。

本発明に係る化合物 (I-31) は、例えば、以下の方法によっても製造す
25 ることができる。



〔式中、 n は、1又は2を示し、 Y は脱離基を示し、他の記号は前記と同じ〕

(工程 3 6) 本工程は、塩基及び金属触媒の存在下、前記記載の化合物 (2 7) と化合物 (3 6) とを反応させて、化合物 (3 7) を製造する方法である。

5 L^1 、 L^2 としては、より具体的には、例えば、フッ素、塩素、臭素、ヨウ素等のハロゲンが挙げられる。

M^1 は、化合物 (2 7) と化合物 (3 6) との反応において、化合物 (3 7) を製造するものであれば、いかなるものを用いてもよいが、具体的には、例えば、トリアルキルスズ、ボロン酸、ボロン酸エステル等が挙げられる。化合物

10 (3 6) としては、より具体的には、例えば、トリメチルー (ピリジン-2-イル) スズ又は1-(tert-ブトキシカルボニル) ピロール-2-ボロン酸等が挙げられる。

化合物(36)として、トリメチルー(ピリジン-2-イル)スズを用いる場合には、例えば、いわゆるS t i l l e反応を用いて行う方法が挙げられる。

また、化合物(36)として、1-(tert-ブトキシカルボニル)ピロール-2-ボロン酸を用いる場合には、例えば、いわゆる鈴木反応を用いて
5 行う方法が挙げられる。

用いられる化合物(36)の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物(27)1当量に対して、通常0.1乃至50当量、好ましくは、0.2乃至10当量である。

用いられる塩基の量は、用いられる化合物及び溶媒の種類その他の反応条件
10 により異なるが、通常0.1乃至20当量、好ましくは0.5乃至5当量である。

用いられる塩基としては、本工程において、化合物(27)と化合物(36)との反応において、化合物(37)を製造するものであれば、いかなるものを用いてもよいが、例えば、水素化ナトリウム、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム tert-ブトキシド、トリエチルアミン等が挙げられる。
15

用いられる金属触媒の量は、用いられる化合物及び溶媒の種類その他の反応条件により異なるが、通常0.01乃至10当量、好ましくは0.05乃至5当量である。

20 用いられる金属触媒としては、本工程において、化合物(27)と化合物(36)との反応において、化合物(37)を製造するものであれば、いかなるものを用いてもよいが、例えば、テトラキストリフェニルホスフィンパラジウム、ジクロロビス(トリフェニルホスフィン)パラジウム、ジクロロ(1,1'-ビス(ジフェニルホスフィノ)フェロセン)パラジウム等が挙げられる。

25 本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばエチレングリコールジメチルエーテル、水、トルエン、テトラヒドロフラン、N,N-ジメチルホルムアミド、1,4-ジオキサン、ベンゼン、アセトン等が挙げられる。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは

室温乃至150度である。

本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至12時間である。

このようにして得られる化合物(37)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程37)本工程は、化合物(37)と前記化合物(A-1)とを反応させて、化合物(38)を製造する方法である。

本工程における反応は、前記工程27と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物(38)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程38)本工程は、化合物(38)のヘテロ芳香環及びニトロ基を水素雰囲気下、金属触媒にて還元し、必要に応じて保護基を導入して、化合物(39)を製造する方法である。

用いられる還元剤の量は、通常0.01乃至10当量、好ましくは0.1乃至1当量である。

用いられる還元剤としては、本工程において、化合物(38)から、化合物(39)を製造するものであれば、いかなるものを用いてもよいが、例えば、10%白金-炭素、白金-ブラックなどが挙げられる。

本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばメタノール、エタノール、テトラヒドロフラン、1,4-ジオキサン、酢酸エチル等が挙げられる。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは室温乃至150度である。

本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至12時間である。

本工程における反応圧力は、通常常圧乃至100気圧、好ましくは常圧乃至

20気圧である。

このようにして得られる化合物(39)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

- 5 (工程39) 本工程は、化合物(39)にニトロ基を導入して、化合物(40)を製造する方法である。本工程における反応は、前記工程29と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。必要に応じて、 R_p^1 を変換することができる。

- 10 このようにして得られる化合物(40)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

- (工程40) 本工程は、化合物(40)の有するニトロ基を還元して、化合物(41)を製造する方法である。本工程における反応は、前記工程31と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。
- 15

このようにして得られる化合物(41)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

- (工程41) 本工程は、化合物(41)と前記化合物(5)とを反応させて化合物(42)を製造するか、或いは、化合物(41)と前記化合物(6)とを反応させ、次いで環化反応に付すことにより化合物(42)を製造する方法である。
- 20

- 化合物(41)と前記化合物(5)との反応は、前記工程32と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。
- 25

また、化合物(41)と前記化合物(6)とを反応させ、次いで、環化させる反応は、前記工程33-1及び33-2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物(42)は、公知の分離精製手段、例えば濃

縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 4 2) 本工程は、得られた化合物 (4 2) の有するアミノ基の保護基 Rp^1 を除去して、化合物 (4 3) を製造する方法である。

- 5 アミノ基の保護基 Rp^1 の除去方法は、前記文献記載の方法 (例えばプロテクトイブグループス イン オーガニック シンセシス (Protective Groups in Organic Synthesis)、T. W. Green 著、第 2 版、John Wiley & Sons 社、1991 年、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。
- 10 きる。

このようにして得られる化合物 (4 3) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

- (工程 4 3) 本工程は、化合物 (4 3) と化合物 (F) とを反応させること
- 15 により本発明に係る化合物 (I-3) を製造する方法である。本工程におけるアミノ基の保護基 R^4 の導入は前記記載の文献 (例えばプロテクトイブグループス イン オーガニック シンセシス (Protective Groups in Organic Synthesis)、T. W. Green 著、第 2 版、John Wiley & Sons 社、1991 年、等)、それに準じた方法
- 20 又はこれらと常法とを組み合わせることにより行うことができる。

R^4 としては、より具体的にはアルキル、アルキルアミド、カルバモイル、アルキルカルバモイル、アルキルカーバメート等が挙げられる。

- 化合物 (F) としては、具体的には、例えば、無水酢酸、無水トリフルオロ酢酸、プロピオン酸、クロロ酢酸、アクリル酸エチル、塩化メタンシルホニル、
- 25 臭化ベンジル等が挙げられる。

用いられる化合物 (F) の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物 (4 3) 1 当量に対して、通常 0.1 乃至 2.0 当量、好ましくは 0.5 乃至 5 当量である。

本工程において用いられる反応溶媒は、反応に支障のないものであれば、特

に限定されないが、例えばジクロロメタン、クロロホルム、テトラヒドロフラン、アセトニトリル、ジメチルホルムアミド、ベンゼン、アセトン、エタノール、2-プロパノール等が挙げられる。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは
5 室温乃至150度である。

本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至12時間である。

また、上記化合物(39)と(6)とを反応させた後、ニトロ基を導入し、最後に該ニトロ基をアミノ基に還元すると同時に環化を行うか、もしくは必要
10 に応じて別途環化反応を行うことによっても、本発明に係る化合物(I-31)を製造することができる。

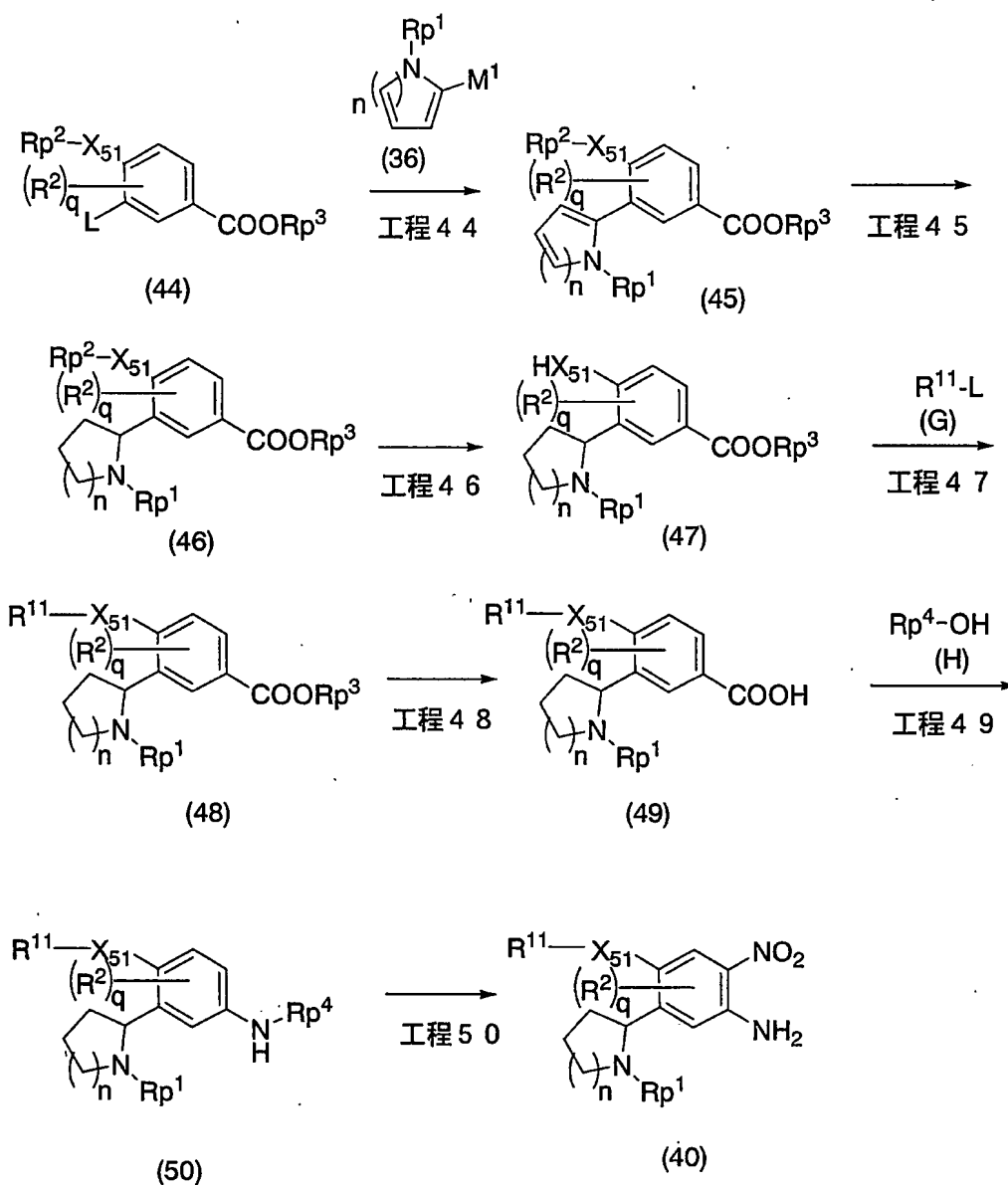
なお、化合物(39)と化合物(6)とのアミド化、ニトロ化、ニトロ基からアミノ基への還元及び環化反応は、それぞれ、工程5-1、工程13、工程3及び工程5-1と同様の方法、これに準じた方法又はこれらと常法とを組み
15 合わせることにより行うことができる。

このようにして得られる本発明に係る化合物(I-31)は、公知の分離精製手段、例えば濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製することができる。

なお、化合物(42)において、アミノ基の保護基 R_p^1 が所望の R^4 に該当
20 する場合には、以後の工程42及び43を行うことなく、化合物(42)が本発明に係る化合物である。

また、化合物(43)が所望の化合物である場合には、工程43を行うことなく、化合物(43)が本発明に係る化合物となる。

本発明に係る化合物(I-31)は以下の方法によっても製造することができる。
25



[式中、 Rp^2 、 Rp^3 及び Rp^4 は、それぞれ保護基を示し、 L は脱離基を示し、他の記号は前記と同じ]

- (工程 4 4) 本工程は、化合物 (4 4) と前記化合物 (3 6) とを反応させることにより、化合物 (4 5) を製造する方法である。 Rp^2 は、 X_{51} の保護基を示し、具体的には、例えば、メトキシメチル、メチル、ベンジル、4-メトキシベンジル、2-(トリメチルシリル)エトキシメチル、2-(トリメチルシリル)エチル、tert-ブチルジメチルシリル、tert-ブチルカルボニル等が挙げられる。また、 Rp^3 は、カルボキシルの保護を示し、具体的に

- は、例えば、メトキシメチル、メチル、エチル、tert-ブチル、ベンジル、4-メトキシベンジル、2-(トリメチルシリル)エチル、tert-ブチルジメチルシリル等が挙げられる。R^{p4}は、不活性なアルキルを示し、具体的には、例えば、メチル、エチル、tert-ブチル、ベンジル、4-メトキシベンジル、2-(トリメチルシリル)エチル等が挙げられる。本工程における反応は、前記工程36と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。このようにして得られる化合物(45)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程45)本工程は、前記工程で得られた化合物(45)のヘテロ芳香環を水素雰囲気下、金属触媒にて還元し、化合物(46)を製造する方法である。

用いられる還元剤の量は、通常0.01乃至10当量、好ましくは0.05乃至1当量である。

- 15 用いられる還元剤としては、本工程において、化合物(45)から、化合物(46)を製造するものであれば、いかなるものを用いてもよいが、例えば、10%白金-炭素、白金ブラックなどが挙げられる。

- 本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばメタノール、エタノール、テトラヒドロフラン、N,N-ジメチルホルムアミド、1,4-ジオキサン、酢酸エチル等が挙げられる。

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは室温乃至150度である。

本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至12時間である。

- 25 本工程における反応圧力は、通常常圧乃至100気圧、好ましくは常圧乃至20気圧である。

このようにして得られる化合物(46)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。

(工程 4 6) 本工程は、化合物 (4 6) の有する保護基 Rp^2 を除去して、化合物 (4 7) を製造する方法である。本工程における保護基の除去は、文献記載の方法 (例えばプロテクティブ グループス イン オーガニック シンセシス (Protective Groups in Organic Synthesis)、T. W. Green 著、第 2 版、John Wiley & Sons 社、1991 年、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができ、 Rp^2 がメトキシメチルの場合には、該保護基の除去は、例えば、トリフルオロ酢酸等を用いることにより行うことができる。

- 10 Rp^1 の除去にトリフルオロ酢酸を用いる場合には、触媒の量は、通常 0. 01 乃至 1000 当量、好ましくは 0. 1 乃至 10 当量である。

本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばクロロホルム等が挙げられる。

- 15 反応温度は、通常室温乃至反応溶媒の還流温度、好ましくは室温乃至 100 度である。

反応時間は、通常 0. 1 時間乃至 72 時間、好ましくは 0. 5 時間乃至 12 時間である。

- 20 このようにして得られる化合物 (4 7) は、公知の分離精製手段、例えば、濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく、次工程に付すことができる。必要に応じて、 Rp^1 を変換することができる。

- 25 (工程 4 7) 本工程は、化合物 (4 7) と化合物 (G) とを反応させることにより、化合物 (4 8) を製造する方法である。ここで、L は脱離基を示し、前記 L_1 や L_2 と同様の基が挙げられる。化合物 (G) としては、具体的には、例えば、臭化ベンジル、4-フルオローベンゾニトリル、4-フルオローベンズアルデヒド等が挙げられる。本工程における反応は、前記工程 2 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。このようにして得られる化合物 (4 8) は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー

等により単離精製するか又は単離精製することなく、次工程に付することができる。

(工程 4 8) 本工程は、化合物 (4 8) の有するカルボキシルの保護基 $R p^3$ を除去して、化合物 (4 9) を製造する方法である。化合物 (4 8) の有するカルボキシルの保護基としては、前記工程 4 4 乃至 4 7 においてカルボキシルの保護基として作用し、かつ、工程 4 8 において容易に除去することができるものであれば、いかなるものであってもよいが、例えばメチル、エチル、tert-ブチル等の直鎖又は分岐を有する低級アルキル、2-ヨウ化エチル、2, 2, 2-トリクロロエチル等のハロゲン化低級アルキル、アリル、2-プロペニル、2-メチル-2-プロペニル等の低級アルケニル、ベンジル、パラメトキシベンジル等のアラルキル等を挙げることができる。

このようなカルボキシルの保護基 $R p^3$ の導入及び除去方法については、文献記載の方法 (例えばプロテクティブ グループス イン オーガニック シンセシス (Protective Groups in Organic Synthesis)、T. W. Green 著、第 2 版、John Wiley & Sons 社、1991 年、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

このようにして得られる化合物 (4 9) は、公知の分離精製手段、例えば濃縮、減圧濃縮、溶媒抽出、結晶化、再沈殿、クロマトグラフィー等により単離精製するか又は単離精製することなく次工程に付することができる。

(工程 4 9) 本工程は、化合物 (4 9) と化合物 (H) とを反応させることにより、化合物 (5 0) を製造する方法であり、例えば、いわゆるクルチウス (Curtius) 転移反応であり、塩基存在下、リン酸アジド化合物及びアルコール化合物 (17-1) を用いて、文献記載の方法 (例えばテトラヘドロン (Tetrahedron)、第 31 巻、1974 年、p 2151-2157、等)、それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

用いられるアルコール化合物 (H) の量は、用いられる化合物及び溶媒の種類、その他の反応条件により異なるが、化合物 (4 9) 1 当量に対して、通常

0.1乃至20当量、好ましくは0.5乃至5当量である。

用いられる塩基の量は、用いられる化合物及び溶媒の種類その他の反応条件により異なるが、通常0.1乃至20当量、好ましくは0.5乃至5当量である。

- 5 用いられるリン酸アジド化合物としては、本工程において、化合物(49)と化合物(H)との反応において、化合物(50)を製造するものであれば、いかなるものを用いてもよいが、例えば、ジエチルリン酸アジド、ジフェニルリン酸アジド等が挙げられる。

- 用いられる塩基としては、本工程において、化合物(49)と化合物(H)との反応において、化合物(50)を製造するものであれば、いかなるものを用いてもよいが、例えば、水素化ナトリウム、炭酸セシウム、炭酸ナトリウム、炭酸カリウム、リン酸カリウム、酢酸カリウム、カリウム t-ブトキシド、トリエチルアミン等が挙げられる。
- 10

- 本工程において用いられる反応溶媒は、反応に支障のないものであれば、特に限定されないが、例えばトルエン、テトラヒドロフラン、塩化メチレン、クロロホルム、1,4-ジオキサン、ベンゼン等が挙げられる。
- 15

本工程における反応温度は、通常0度乃至反応溶媒の還流温度、好ましくは室温乃至150度である。

- 本工程における反応時間は、通常0.1時間乃至72時間、好ましくは0.5時間乃至12時間である。
- 20

このようにして得られる化合物(50)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精製するか又は単離製精製することなく、次工程に付すことができる。

- (工程50)本工程は、化合物(50)にニトロ基を導入して、前記記載の化合物(40)を製造する方法である。本工程における反応は、前記工程29と同様の方法、これに準じた方法又はこれらと常法とを組み合わせで行うことができる。
- 25

このようにして得られる化合物(40)は、公知の分離精製手段、例えば濃縮、減圧濃縮、結晶化、溶媒抽出、再沈殿、クロマトグラフィー等により単離精

製するか又は単離精製することなく、前記工程 40 乃至 43 の方法によって、本発明に係る化合物 (I-3) を製造することができる。

また、上記化合物 (50) において、 Rp^4 を除去し、該アニリン誘導体とした後、該アニリン誘導体と化合物 (6) とを反応させた後、ニトロ基を導入し、
5 最後に該ニトロ基をアミノ基に還元すると同時に環化を行うか、もしくは必要に応じて別途環化反応を行うことによっても、本発明に係る化合物 (I-31) を製造することができる。

なお、化合物 (50) と化合物 (6) とのアミド化、ニトロ化、ニトロ基からアミノ基への還元及び環化反応は、それぞれ、工程 5-1、工程 13、工程
10 3 及び工程 5-1 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより行うことができ、 Rp^4 を除去は、前記記載のプロテクティブ グループス イン オーガニック シンセシス (Protective Groups in Organic Synthesis)、T. W. Green 著、第 2 版、John Wiley & Sons 社、1991 年、等)、
15 それに準じた方法又はこれらと常法とを組み合わせることにより行うことができる。

本発明によって提供される新規 2-ヘテロアリアル置換ベンズイミダゾール誘導体は、薬学的に許容される塩として存在することができ、当該塩は、本発明に係る化合物 (I-0) 及び (I-0) に包含される上記式 (I-1)、
20 (I-11)、(I-12)、(I-2)、(I-11-0)、(I-31) 及び (I-4) を用いて、常法に従って製造することができる。

具体的には、上記 (I-0)、(I-1)、(I-11)、(I-12)、(I-2)、(I-11-0)、(I-31) 及び (I-4) の化合物が、当該分子内に例えばアミノ基、ピリジル基等に由来する塩基性基を有している場合
25 には、当該化合物を酸で処理することにより、相当する薬学的に許容される塩に変換することができる。

当該酸付加塩としては、例えば塩酸塩、フッ化水素酸塩、臭化水素酸塩、ヨウ化水素酸塩等のハロゲン化水素酸塩；硝酸塩、過塩素酸塩、硫酸塩、リン酸塩、炭酸塩等の無機酸塩；メタンスルホン酸塩、トリフルオロメタンスルホン酸塩、

エタンスルホン酸塩等の低級アルキルスルホン酸塩；ベンゼンスルホン酸塩、
p-トルエンスルホン酸塩等のアリールスルホン酸塩；フマル酸塩、コハク酸
塩、クエン酸塩、酒石酸塩、シュウ酸塩、マレイン酸塩等の有機酸塩；及びグ
ルタミン酸塩、アスパラギン酸塩等のアミノ酸等の有機酸である酸付加塩を挙
5 げることができる。また、本発明の化合物が酸性基を当該基内に有している場
合、例えばカルボキシル基等を有している場合には、当該化合物を塩基で処理
することによっても、相当する薬学的に許容される塩に変換することができる。
当該塩基付加塩としては、例えばナトリウム、カリウム等のアルカリ金属塩、
カルシウム、マグネシウム等のアルカリ土類金属塩、アンモニウム塩、グアニ
10 ジン、トリエチルアミン、ジシクロヘキシルアミン等の有機塩基による塩が挙
げられる。さらに本発明の化合物は、遊離化合物又はその塩の任意の水和物又
は溶媒和物として存在してもよい。

2型糖尿病或いはそれに関連する疾患若しくは症状の予防又は治療のための
薬剤を製造するにあたり、本発明に係る式（I）の化合物は、式（I）の化合
15 物と担体物質とを組み合わせ用いることができる。

本発明に係る式（I）の化合物の予防又は治療のための投与量は、もちろん、
治療する症状の性質、選択する特定の化合物及び投与経路により変動する。

また、年齢、体重及び各患者の感受性によっても変動する。一般的に、1日
の投与量は、単回又は複数回の量として、体重1kgあたり、約0.001m
20 gから約100mgであり、好ましくは、体重1kgあたり、約0.01mg
から約50mgであり、より好ましくは約0.1mgから10mgである。こ
れらの制限を越えた範囲での投与量の使用が必要な場合もありうる。

適切な経口投与量の例としては、単回又は1日あたり、2乃至4回の複数回
投与としては、少なくとも約0.01mgから多くとも2.0gである。好ま
25 しくは、投与量の範囲は、1日に1回又は2回の投与で、約1.0mgから約
200mgである。より好ましくは、投与量の範囲は、1日1回の投与で約1
0mgから100mgである。

静脈内投与又は経口投与を用いた場合には、代表的な投与範囲は、1日あた
り、体重1kgあたり、式（I）の化合物を約0.001mgから約100m

g（好ましくは0.01mgから約10mg）であり、より好ましくは1日あたり、体重1kgあたり、式（I）の化合物を約0.1mgから10mgである。

上述したように、医薬組成物は、式（I）の化合物と薬学的に許容される担体を含む。「組成物」という用語は、直接又は間接的に、2又はそれ以上のい
5 かなる成分を組み合わせ、複合させ又は凝集させてできたもの、1又はそれ以上の成分を解離させた結果できたもの、或いは、成分間の他のタイプの作用又は相互作用の結果によりできたものだけでなく、担体を構成する活性及び不活性成分（薬学的に許容される賦形剤）も含む。

10 医薬上許容される担体と組み合わせて、2型糖尿病の治療、予防或いはその発症を遅らせるのに有効な量の式（I）の化合物が含まれる組成物が好ましい。

本発明に係る化合物の効果的な量を哺乳類、とりわけヒトに投与するためには、いかなる適切な投与経路でも用いることができる。例えば、経口、直腸、局所、静脈、眼、肺、鼻などを用いることができる。投与形態の例としては、
15 錠剤、トローチ、散剤、懸濁液、溶液、カプセル剤、クリーム、エアロゾルなどがあり、経口用の錠剤が好ましい。

経口用の組成物を調製するに際しては、通常の医薬用媒体であれば、いかなるものも用いることができ、そのような例としては、例えば、水、グリコール、オイル、アルコール、香料添加剤、保存料、着色料などであり、経口用の液体
20 組成物を調製する場合には、例えば、懸濁液、エリキシル剤及び溶液が挙げられ、担体としては、例えば、澱粉、砂糖、微結晶性セルロース、希釈剤、造粒剤、潤滑剤、結合剤、崩壊剤などが挙げられ、経口用の固体組成物を調製する場合には、例えば、パウダー、カプセル剤、錠剤などが挙げられ、中でも経口用の固体組成物が好ましい。

25 投与のしやすさから、錠剤やカプセル剤が最も有利な経口投与形態である。必要ならば、錠剤は、標準の水性又は非水性の技術でコーティングすることができる。

上記の通常の投与形態に加えて、式（I）に係る化合物は、例えば、U. S. 特許番号3, 845, 770、3, 916, 899、3, 536, 809、3,

598, 123, 3, 630, 200及び4, 008, 719に記載の放出制御手段及び／又はデリバリー装置によっても、投与することができる。

経口投与に適した本発明に係る医薬組成物は、パウダー又は顆粒として、或いは水溶性の液体、非水溶性の液体、水中油型のエマルジョン又は油中水型のエマルジョンとして、それぞれがあらかじめ決められた量の活性成分を含むカプセル剤、カシュ剤又は錠剤を挙げることができる。そのような組成物は、薬剤学上いかなる方法を用いて調製することができるが、すべての方法は、活性成分と1又は2以上の必要な成分からなる担体とを一緒にする方法も含まれる。

- 10 一般に、活性成分と液体の担体又はよく分離された固体の担体或いは両方とを均一かつ十分に混合し、次いで、必要ならば、生産物を適当な形にすることにより、組成物は調製される。例えば、錠剤は、圧縮と成形により、必要に応じて、1又は2以上の副成分と共に調製される。圧縮錠剤は、適当な機械で、必要に応じて、結合剤、潤滑剤、不活性な賦形剤、界面活性剤又は分散剤と混合して、活性成分をパウダーや顆粒などの形に自由自在に圧縮することにより調製される。

成形された錠剤は、パウダー状の湿った化合物と不活性な液体の希釈剤との混合物を適当な機械で成形することにより調製される。

- 20 好ましくは、各錠剤は、活性成分を約1mg乃至1g含み、各カシュ剤又はカプセル剤は、活性成分を約1mg乃至500mg含む。

式(I)の化合物についての医薬上の投与形態の例は、次の通りである。

[表1]

注射用懸濁液 (I.
M.)

	mg/ml
式(I)の化合物	10
メチルセルロース	5.0
Tween 80	0.5
ベンジルアルコール	9.0
塩化ベンズアルコニウム	1.0

注射用水を加えて、1.0ml とする。

[表 2]

錠剤

	mg/tablet
式 (I) の化合物	25
メチルセルロース	415
Tween 80	14.0
ベンジルアルコール	43.5
ステアリン酸マグネシウム	2.5

合計 500mg

[表 3]

カプセル剤

	mg/capsule
式 (I) の化合物	25
ラクトースパウダー	573.5
ステアリン酸マグネシウム	1.5

合計 600mg

5

[表 4]

エアロゾール

	1 容器あたり
式 (I) の化合物	24mg
レシチン、NF Liq. Conc.	1.2mg
トリクロロフルオロメタン、NF	4.025g
ジクロロジフルオロメタン、NF	12.15g

- 10 式 (I) の化合物は、2 型糖尿病と関連する疾患又は症状だけでなく、2 型糖尿病の発症の治療／予防／遅延に用いられる他の薬剤と組み合わせて用いることができる。該他の薬剤は、通常用いられる投与経路又は投与量で、式 (I) の化合物と同時に又は別々に投与することができる。

式 (I) の化合物は、1 又は 2 以上の薬剤と同時に使用する場合には、式

(I) の化合物とこれらの他の薬剤とを含んだ医薬組成物が好ましい。従って、本発明に係る医薬組成物は、式 (I) の化合物に加えて、1又は2以上の他の活性成分も含む。式 (I) の化合物と組み合わせて用いられる活性成分の例としては、別々に投与するか、又は同じ医薬組成物で投与してもよいが、以下のものに限定されることはない。

(a) ビスーグアニド (例、ブホルミン、メトホルミン、フェンホルミン)

(b) PPARアゴニスト (例、トログリタゾン、ピオグリタゾン、ノシグリタゾン)

(c) インスリン

10 (d) ソマトスタチン

(e) α -グルコシダーゼ阻害剤 (例、ボグリボース、ミグリトール、アカルボース)、

(f) インスリン分泌促進剤 (例、アセトヘキサミド、カルブタミド、クロルプロバミド、グリボムリド、グリクラジド、グリメルピリド、グリピジド、グリキジン、グリソキセピド、グリブリド、グリヘキサミド、グリピナミド、フェンブタミド、トラザミド、トルブタミド、トルシクラミド、ナテグリニド、レバグリニド)、及び

(g) DPP-IV (ジペプチジルペプチダーゼ IV) 阻害剤

2番目の活性成分に対する式 (I) の化合物の重量比は、幅広い制限の範囲内で変動し、さらに、各活性成分の有効量に依存する。従って、例えば、式 (I) の化合物をPPARアゴニストと組み合わせて用いる場合には、式 (I) の化合物のPPARアゴニストに対する重量比は、一般的に、約1000:1乃至1:1000であり、好ましくは、約200:1乃至1:200である。式 (I) の化合物と他の活性成分との組み合わせは、前述の範囲内であるが、いずれの場合にも、各活性成分の有効量が用いられるべきである。

次に本発明に係る化合物 (I) で表される化合物が示すグルコキナーゼ活性化能及びその試験方法について示す。

前記式 (I) で表される化合物の有する優れたグルコキナーゼ活性化作用の測定は、文献記載の方法 (例えば、ディアベテス (Diabetes)、第4

5 巻、第1671頁－1677頁、1996年等）又はそれに準じた方法によって行うことができる。

グルコキナーゼ活性は、グルコース－6－リン酸を直接測定するのではなく、リポーターエンザイムであるグルコース－6－リン酸デヒドロゲナーゼがグル
5 コース－6－リン酸からホスホグルコノラクトンを生成する際に、生じるThi
io－NADHの量を測定することによって、グルコキナーゼの活性化の程度を調べる。

このアッセイで使用するrecombinant human liver GKはFLAG fusion proteinとしてE. coliに発現させ、ANTI FLAG M2 AFFINITY GEL (Sigma) で精
10 製した。

アッセイは平底96-well plateを用いて30℃で行った。Assay buffer (25mM Hepes Buffer: pH=7. 2、2mM MgCl₂、1mM ATP、0. 5mM TNAD、1mM dithiothreitol) を69μl分注し、化合物のDMSO溶液またはコントロールとしてDMSOを1μl加えた。次に、氷中で冷やしておいたEnzyme mixture (FLAG-GK、20U/ml G6PDH) 20
15 μlを分注した後、基質である25mMグルコースを10μl加え、反応を開始させる（最終グルコース濃度=2. 5mM）。

20 反応開始後、405nmの吸光度の増加を30秒ごとに10分間測定し、最初の5分間の増加分を使用して化合物の評価を行った。FLAG-GKは1% DMSO存在下で5分後の吸光度増加分が0. 05から0. 1の間になるように加えた。

DMSOコントロールでのOD値を100%とし、評価化合物の各濃度におけるOD値を測定した。各濃度のOD値より、E_{max} (%) 及びEC₅₀ (μM) を算出し、化合物のGK活性化能の指標として用いた。
25

本方法により本発明に係る化合物のGK活性化能を測定した。その結果を下記表1に示す。

[表5]

(本発明化合物の GK 活性化能)

化合物番号	E _{max} (%)	EC ₅₀ (μ M)
実施例 67	832	1.4
実施例 26	768	2.3
実施例 122	664	1.9

本発明に係る化合物は上記表 1 に示したように、E_{max} 及び EC₅₀ を指標として、優れた GK 活性化能を有している。

実施例

- 以下において、実施例をあげて本発明をさらに具体的に説明するが、本発明は
5 これらによって何ら限定されるものではない。

製剤例 1

製造例 1 の化合物 10 部、重質酸化マグネシウム 15 部及び乳糖 75 部を均一に混合して、350 μm 以下の粉末状又は細粒状の散剤とする。この散剤をカプセル容器に入れてカプセル剤とする。

10 製剤例 2

製造例 1 の化合物 45 部、澱粉 15 部、乳糖 16 部、結晶性セルロース 21 部、ポリビニルアルコール 3 部及び蒸留水 30 部を均一に混合した後、破碎造粒して乾燥し、次いで篩別して直径 1410 乃至 177 μm の大きさの顆粒剤とする。

15 製剤例 3

製剤例 2 と同様の方法で顆粒剤を作製した後、この顆粒剤 96 部に対してステアリン酸カルシウム 3 部を加えて圧縮成形し直径 10 mm の錠剤を作製する。

製剤例 4

- 製剤例 2 の方法で得られた顆粒剤 90 部に対して結晶性セルロース 10 部及び
20 ステアリン酸カルシウム 3 部を加えて圧縮成形し、直径 8 mm の錠剤とした後、これにシロップゼラチン、沈降性炭酸カルシウム混合懸濁液を加えて糖衣錠を作製する。

以下において、製剤例、製造例、参考例により本発明をさらに具体的に説明するが、本発明はこれらによって何ら限定されるものではない。

- 25 実施例の薄層クロマトグラフは、プレートとして Silicagel 60

F₂₄₅ (Merck) を、検出法としてUV検出器を用いた。カラム用シリカゲルとしては、Wakogel™ C-300 (和光純薬) を、逆相カラム用シリカゲルとしては、LC-SORB™ SP-B-ODS (Chemco) 又はYMC-GEL™ ODS-AQ 120-S50 (山村化学研究所) を用

5 いた。

下記の実施例における略号の意味を以下に示す。

- i-Bu : イソブチル
- n-Bu : n-ブチル
- t-Bu : t-ブチル
- 10 Me : メチル
- Et : エチル
- Ph : フェニル
- i-Pr : イソプロピル
- n-Pr : n-プロピル
- 15 CCl₃ : 重クロロホルム
- CD₃OD : 重メタノール
- DMSO-d₆ : 重ジメチルスルホキシド

下記に核磁気共鳴スペクトルにおける略号の意味を示す。

- s : シングレット
- 20 d : ダブレット
- dd : ダブルダブレット
- t : トリプレット
- m : マルチプレット
- br : ブロード
- 25 q : カルテット
- J : カップリング定数
- Hz : ヘルツ

実施例 1

2-ピリジン-2-イル-5, 6-ビス(ピリジン-3-イルオキシ)-1H-
-ベンズイミダゾール

(工程1)

3-(2-フルオロ-4-ニトロ-フェノキシ)-ピリジンの合成

- 5 3, 4-ジフルオロニトロベンゼン 3.18 g のジメチルホルムアミド 20 ml 溶液に、3-ヒドロキシピリジン 2.09 g、及び炭酸カリウム 5.52 g を加え、反応液を 90 度にて 1 時間攪拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開
10 溶媒：ヘキサン／酢酸エチル＝9／1）にて精製し、表題化合物を得た。

(工程2)

5-フルオロ-2-ニトロ-4-(ピリジン-3-イルオキシ)-フェニル
アミンの合成

- 15 3-(2-フルオロ-4-ニトロ-フェノキシ)-ピリジン 4.72 g のメタノール 30 ml 溶液に、20%水酸化パラジウム-炭素触媒 1.0 g を加え、反応液を水素雰囲気下、5 時間攪拌した。触媒を濾去後、溶媒を減圧留去し、粗生成物を得た。得られた粗生成物のトリフルオロ酢酸 40 ml 溶液に、硝酸カリウム 1.88 g を加え、反応液を室温にて一終夜攪拌した後、溶媒を減圧留去した。残渣を酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗
20 浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝4／1）にて精製し、表題化合物を得た。

(工程3)

- 25 4, 5-ビス-(ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミンの合成

3-(2-フルオロ-4-ニトロ-フェノキシ)-ピリジン 680 mg のジメチルホルムアミド 8 ml 溶液に、3-ヒドロキシピリジン 285 mg、及び炭酸カリウム 829 mg を加え、反応液を 90 度にて 2 時間攪拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネ

シウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルガラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／1～酢酸エチル）にて精製し、粗生成物を得た。得られた粗生成物のエタノール10ml溶液に、展開ラネーニッケル触媒500mgを加え、反応液を水素雰囲気下、2時間攪拌した。触媒を濾去後、溶媒を減圧留去することで、表題化合物を得た。

（工程4）

2-ピリジン-2-イル-5, 6-ビス（ピリジン-3-イルオキシ）-1H-ベンズイミダゾールの製造

4, 5-ビス（ピリジン-3-イルオキシ）-ベンゼン-1, 2-ジアミン30mgのニトロベンゼン0.3ml溶液に、ピリジン-2-カルボキサアルデヒド0.01mlを120度にて加え、反応液を同温度にて2時間攪拌した。反応混合物を、逆相中圧液体クロマトグラフィー〔ODS-AS-360-CC（YMC社製）移動相：水-アセトニトリル-0.1%トリフルオロ酢酸〕にて精製した。得られたフラクションの溶媒を減圧留去した後、分取用薄層クロマトグラフィー（KieselgelTM 60 F₂₅₄, Art 5744（メルク社製）、クロロホルム／メタノール＝20／1）にて精製し、表題化合物を黄色油状物質として得た。

¹H NMR (CDCl₃) δ: 7.10-7.40 (4H, m), 7.28 (1H, s), 7.38 (1H, ddd, J=1.2 Hz, 4.8 Hz, 7.6 Hz), 7.62 (1H, s), 7.87 (1H, td, J=7.6 Hz, 1.2 Hz), 8.12-8.40 (4H, m), 8.38 (1H, d, J=7.6 Hz), 8.63 (1H, d, J=4.8 Hz), 10.8 (1H, brs)

ESI-MS (m/e): 382 [M+H]

25 実施例2

5-（2-ヒドロキシメチル-フェノキシ）-2-ピリジン-2-イル-6-（ピリジン-3-イルオキシ）-1H-ベンズイミダゾール

実施例1（工程2）で得られた5-フルオロ-2-ニトロ-4-（ピリジン-3-イルオキシ）-フェニルアミン、及び2-ヒドロキシメチル-フェノー

ルを用いて、実施例1と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 4.45 (2H, s), 6.76 (1H, d, $J=8.0\text{ Hz}$), 7.04 (1H, t, $J=6.8\text{ Hz}$), 7.08–7.30 (5H, m), 7.30–7.43 (2H, m), 7.86 (1H, td, $J=8.0\text{ Hz}$, 2.4 Hz), 8.18–8.32 (1H, m), 8.22 (1H, s), 7.36 (1H, d, $J=7.6\text{ Hz}$), 8.62 (1H, d, $J=8.4\text{ Hz}$), 10.54 (1H, brs)
ESI-MS (m/e): 411 [M+H]

10

実施例3

5-(2-(1-ヒドロキシ-エチル)-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

2-(1-ヒドロキシ-エチル)-フェノールを用いて、実施例2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.25–1.34 (6H, m), 4.80–4.96 (1H, m), 7.76 (1H, dd, $J=4.4\text{ Hz}$, 8.0 Hz), 7.02–7.34 (6H, m), 7.38 (1H, t, $J=6.4\text{ Hz}$), 7.42–7.60 (1H, m), 7.87 (1H, td, $J=7.6\text{ Hz}$, 1.6 Hz), 8.20–8.34 (2H, m), 8.39 (1H, d, $J=7.6\text{ Hz}$), 8.60–8.64 (1H, m), 10.72 (1H, brs)

ESI-MS (m/e): 425 [M+H]

25

実施例4

5-(2-アセチル-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

2-アセチル-フェノールを用いて、実施例2と同様の方法、これに準じた

方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.22–2.50 (3H, m), 6.81 (1H, d, $J=8.4\text{ Hz}$), 7.00–7.45 (4H, m), 7.45–7.95 (5H, m), 8.20–8.35 (2H, m), 8.37 (1H, d, $J=7.6\text{ Hz}$), 8.60–8.70 (1H, m), 10.49 (1H, br s)

ESI-MS (m/e): 423 $[\text{M}+\text{H}]$

10 実施例 5

5-(2-シアノフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

2-ヒドロキシベンゾニトリルを用いて、実施例 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 6.80 (1H, t, $J=8.0\text{ Hz}$), 7.06 (1H, t, $J=7.6\text{ Hz}$), 7.25–7.35 (2H, m), 7.35–7.74 (1H, m), 7.56 (1H, d, $J=7.6\text{ Hz}$), 7.58–7.70 (1H, m), 7.87 (1H, t, $J=7.6\text{ Hz}$), 8.12–8.25 (1H, m), 8.31 (1H, br s), 8.38 (1H, d, $J=8.0\text{ Hz}$), 8.58–8.68 (1H, m), 10.80–11.08 (1H, m)

ESI-MS (m/e): 406 $[\text{M}+\text{H}]$

25 実施例 6

5-(3-シアノフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

3-ヒドロキシベンゾニトリルを用いて、実施例 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 7.02–7.08 (2H, m), 7.14 (1H, d, $J=7.5\text{ Hz}$), 7.20 (1H, dd, $J=4.4\text{ Hz}$, 7.5 Hz), 7.28–7.36 (3H, m), 7.39 (1H, t, $J=5.9\text{ Hz}$), 7.42–7.52 (1H, m), 7.88 (1H, dt, $J=1.6\text{ Hz}$, 7.9 Hz), 8.22 (1H, d, $J=3.6\text{ Hz}$), 8.30 (1H, d, $J=3.6\text{ Hz}$), 8.39 (1H, d, $J=7.9\text{ Hz}$), 8.62 (1H, d, $J=5.9\text{ Hz}$)

ESI-MS (m/e): 406 $[\text{M}+\text{H}]$

10 実施例7

5-(4-シアノフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

4-ヒドロキシベンゾニトリルを用いて、実施例2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 6.84 (2H, d, $J=7.0\text{ Hz}$), 7.04–7.12 (1H, m), 7.12–7.26 (1H, m), 7.26–7.43 (1H, m), 7.30–7.43 (1H, m), 7.51 (2H, d, $J=7.0\text{ Hz}$), 7.44–7.76 (1H, m), 7.78–7.90 (1H, m), 8.12–8.21 (1H, m), 8.21–8.30 (1H, m), 8.30–8.40 (1H, m), 8.43–8.65 (1H, m), 10.88 (1H, brs)

ESI-MS (m/e): 406 $[\text{M}+\text{H}]$

実施例8

5-(4-ジメチルカルバモイルフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

4-ヒドロキシ安息香酸 ジメチルアミドを用いて、実施例2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 3.00 (3H, brs), 3.08 (3H, brs), 6.83 (1H, d, $J=8.8\text{ Hz}$), 6.86 (1H, d, $J=8.8\text{ Hz}$), 7.18–7.23 (2H, m), 7.26–7.36 (3H, m), 7.38–7.42 (1H, m), 7.61 (1H, d, $J=2.5\text{ Hz}$), 7.89 (1H, dd, $J=7.7, 7.7\text{ Hz}$), 8.19–8.38 (2H, m), 8.36 (1H, d, $J=7.7\text{ Hz}$), 8.63 (1H, d, $J=4.8\text{ Hz}$)
ESI-MS (m/e): 452 [M+H]

10 実施例 9

5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

4-メタンスルホニルフェノールを用いて、実施例 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 3.40 (3H, s), 6.96 (2H, d, $J=8.8\text{ Hz}$), 7.10–7.16 (1H, m), 7.17–7.25 (1H, m), 7.32 (1/2H, s), 7.38 (1/2H, s), 7.39–7.43 (1H, m), 7.65 (1/2H, s), 7.70 (1/2H, s), 7.83 (2H, dd, $J=8.8, 3.1\text{ Hz}$), 7.90 (1H, ddd, $J=7.8, 7.8, 1.7\text{ Hz}$), 8.23 (1H, brs), 8.32 (1H, brs), 8.39 (1H, d, $J=7.8\text{ Hz}$), 8.65 (1H, d, $J=4.7\text{ Hz}$), 10.84 (1H, brs)
ESI-MS (m/e): 459 [M+H]

25

実施例 10

5-(4-メトキシカルボニルフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

4-ヒドロキシ安息香酸 メチルエステルを用いて、実施例 2 と同様の方

法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 3.88 (3H, s), 6.82 (2H, d, $J=8.8\text{ Hz}$), 7.12 (1H, ddd, $J=8.6, 2.9, 1.5\text{ Hz}$), 7.18 (1H, dd, $J=8.6, 4.8\text{ Hz}$), 7.28 (1H, brs), 7.32 (1H, brs), 7.87 (1H, ddd, $J=7.7, 7.7, 1.8\text{ Hz}$), 7.92 (2H, d, $J=8.8\text{ Hz}$), 8.20 (1H, d, $J=2.9\text{ Hz}$), 8.27 (1H, d, $J=4.8\text{ Hz}$), 8.37 (1H, dd, $J=7.7, 1.1\text{ Hz}$), 8.61 (1H, dd, $J=5.1, 1.8\text{ Hz}$), 10.80 (1H, brs)
ESI-MS (m/e): 439 $[\text{M}+\text{H}]$

実施例 11

5-(2-ホルミルフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

2-ヒドロキシベンズアルデヒドを用いて、実施例 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 6.80 (1H, d, $J=8.4\text{ Hz}$), 6.92-7.58 (6H, m), 7.83 (1H, d, $J=8.0\text{ Hz}$), 7.87 (1H, td, $J=7.6\text{ Hz}, 1.2\text{ Hz}$), 8.12-8.34 (3H, m), 8.39 (1H, d, $J=8.4\text{ Hz}$), 8.55-8.67 (1H, m), 10.06 (1H, s)
ESI-MS (m/e): 409 $[\text{M}+\text{H}]$

実施例 12

5-(2-カルボキシフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

2-ヒドロキシ安息香酸を用いて、実施例 2 と同様の方法、これに準じた方

法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- $^1\text{H NMR}$ (CD_3OD) δ : 6.83 (2H, d, $J=8.8\text{ Hz}$), 7.31 (1H, ddd, $J=8.6, 2.9, 1.5\text{ Hz}$), 7.34 (1H, ddd, $J=8.6, 4.8, 0.7\text{ Hz}$), 7.48 (1H, dd, $J=7.7, 4.8\text{ Hz}$), 7.54 (1H, s), 7.56 (1H, s), 7.92 (2H, d, $J=8.8\text{ Hz}$), 7.96 (1H, ddd, $J=7.7, 7.7, 1.5\text{ Hz}$), 8.09 (1H, dd, $J=2.9, 0.7\text{ Hz}$), 8.20 (1H, dd, $J=4.8, 1.5\text{ Hz}$), 8.27 (1H, d, $J=7.7\text{ Hz}$), 8.72 (1H, d, $J=4.8\text{ Hz}$)
- ESI-MS (m/e): 425 $[\text{M}+\text{H}]$

実施例 13

5-(2-メチル-ピリジン-5-イルスルファニル)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 6-メチル-ピリジン-3-チオールを用いて、実施例2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- $^1\text{H NMR}$ (CDCl_3) δ : 2.53 (3H, s), 7.05 (1H, d, $J=7.6\text{ Hz}$), 7.05, 7.36 (tautomer, 1H, s), 7.12-7.24 (2H, m), 7.32-7.36 (1H, m), 7.44, 7.76 (tautomer, 1H, s), 7.50-7.56 (1H, m), 7.83 (1H, t, $J=8.0\text{ Hz}$), 8.26-8.36 (3H, m), 8.45 (1H, s), 8.56 (1H, d, $J=4.4\text{ Hz}$), 11.28-11.40, 11.40-11.50 (tautomer, 1H, br s)
- ESI-MS (m/e): 412 $[\text{M}+\text{H}]$

実施例 14

5-(2-エトキシカルボニル-フェノキシ)-6-(4-メタンスルホニ

ルーフエノキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール

4-メタンスルホニルーフエノール、及び2-ヒドロキシ安息香酸 エチルエステルを順次用いて、実施例1と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

5 $^1\text{H NMR}$ (CDCl_3) δ : 1.19 (3H, t, $J=7.0\text{ Hz}$), 3.03 (3H, s), 4.14 (2H, q, $J=7.0\text{ Hz}$), 6.87 (1H, dd, $J=7.4, 6.3\text{ Hz}$), 7.00 (2H, dd, $J=9.0, 2.2\text{ Hz}$), 7.10-7.17 (1H, m), 7.14 (1/2H, brs), 7.32 (1/2H, brs), 7.37-7.43 (2H, m) 7.49 (1/2H, brs), 7.67 (1/2H, brs), 7.81 (2H, dd, $J=9.0, 2.2\text{ Hz}$), 7.82-7.90 (2H, m), 8.36-8.40 (1H, m), 8.62-8.64 (1H, m), 10.85 (1H, brs)

ESI-MS (m/e): 530 $[\text{M}+\text{H}]$

15

実施例15

5-(2-ジメチルカルバモイルーフエノキシ) - 6-(4-メタンスルホニルーフエノキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール

20 実施例14で得られた4-フルオロ-5-(4-メタンスルホニルーフエノキシ) - 2-ニトロフェニルアミン、及び2-ヒドロキシ安息香酸 ジメチルアミドを順次用いて、実施例14と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 2.58-3.06 (9H, m), 6.83 (1/3H, d, $J=8.6\text{ Hz}$), 6.86 (2/3H, d, $J=8.4\text{ Hz}$), 7.02-7.11 (3H, m), 7.12-7.18 (2H, m), 7.12-7.18 (1/2H, m), 7.23-7.33 (1H, m), 7.23-7.33 (1/2H, m), 7.36-7.40 (1H, m), 7.58 (1/3H, s), 7.64 (2/3H, s), 7.83-7.90 (3H, m), 8.34-8.38 (1H, m), 8.62-8.64 (1H, m),

10. 58 (2/3H, brs), 10. 61 (1/3H, brs)

ESI-MS (m/e) : 529 [M+H]

実施例16

5 5-(2-メトキシフェノキシ)-6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-メトキシフェノールを用いて、実施例15と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CDCl₃) δ : 3. 03 (3H, s), 3. 69 (3H, s),
10 6. 87-6. 95 (3H, m), 7. 00 (1/2H, s), 7. 08 (2H, dd, J=8. 9, 2. 8Hz), 7. 08-7. 38 (1H, m), 7. 31 (1/2H, s), 7. 35 (1/2H, s), 7. 35-7. 38 (1H, m), 7. 64 (1/2H, s), 7. 83 (2H, dd, J=8. 9, 2. 8Hz), 7. 87 (1H, dd, J=7. 8, 1. 6Hz), 8. 3
15 3-8. 38 (1H, m), 8. 60-8. 62 (1H, m), 10. 62 (1/2H, brs), 10. 73 (1/2H, brs)

ESI-MS (m/e) : 488 [M+H]

実施例17

20 5-(2-シアノフェノキシ)-2-ピリジン-2-イル-6-(4-メタンスルホニルフェノキシ)-1H-ベンズイミダゾール

2-ヒドロキシベンゾニトリルを用いて、実施例15と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

25 ¹HNMR (CDCl₃) δ : 6. 78 (1H, d, J=8. 4Hz), 6. 86 (2H, t, J=9. 6Hz), 7. 09 (1H, dd, J=8. 4Hz, 12. 8Hz), 7. 37-7. 55 (4H, m), 7. 62-7. 92 (4H, m), 8. 40 (1H, d, J=8. 4Hz), 8. 64 (1H, d, J=4. 0Hz)

ESI-MS (m/e) : 483 [M+H]

実施例 18

5 5-(4-ジメチルカルバモイル-フェノキシ)-6-フェノキシ-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-ヒドロキシ安息香酸 ジメチルアミド、及びフェノールを順次用いて、実施例 1 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.99 (3H, brs), 3.07 (3H, brs), 6.85-6.88 (4H, m), 6.97-7.14 (1H, m), 7.21-7.27 (3H, m), 7.31-7.37 (3H, m), 7.55 (1/2H, brs), 7.61 (1/2H, brs), 7.84 (1H, ddd, $J=7.7, 7.7, 1.5\text{ Hz}$), 8.35 (1H, d, $J=7.7\text{ Hz}$), 8.61 (1H, brs), 10.48 (1/2H, brs), 10.51 (1/2H, brs)

ESI-MS (m/e) : 451 [M+H]

実施例 19

20 5-(4-ジメチルカルバモイル-フェノキシ)-6-(4-メチルスルファニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 18 で得られた 4-フルオロ-5-(4-ジメチルカルバモイル-フェノキシ)-2-ニトロ-フェニルアミン、及び 4-メチルメルカプト-フェノールを用いて、実施例 1 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 2.44 (3H, s), 2.99 (3H, brs), 3.07 (3H, brs), 6.81 (2H, d, $J=8.4\text{ Hz}$), 6.87 (2H, d, $J=8.4\text{ Hz}$), 7.18 (2H, d, $J=8.4\text{ Hz}$), 7.10-7.28 (1H, m), 7.32-7.35 (1H, m), 7.33 (2H, d, $J=8.4\text{ Hz}$), 7.54 (1/2H, brs), 7.

6.0 (1/2H, brs), 7.84 (1H, dd, $J=7.7, 7.7$ Hz), 8.34 (1H, d, $J=7.7$ Hz), 8.59–8.61 (1H, m), 10.55 (1/2H, brs), 10.60 (1/2H, brs)

ESI-MS (m/e): 497 [M+H]

5

実施例 20

5-(4-ジメチルカルバモイル-フェノキシ)-6-(2-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-メタンスルホニル-フェノールを用いて、実施例 19 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.94 (3/2H, s), 2.99 (3H, brs), 3.03 (3/2H, brs), 3.08 (3H, brs), 6.88–6.93 (3H, m), 7.15–7.22 (1H, m), 7.24 (1/2H, s), 7.34–7.42 (3H, m), 7.39 (1/2H, s), 7.45–7.52 (1H, m), 7.64 (1/2H, s), 7.70 (1/2H, s), 7.86–7.90 (1H, m), 8.00 (1H, d, $J=7.8$ Hz), 8.38 (1H, d, $J=7.8$ Hz), 8.65 (1H, d, $J=3.9$ Hz), 10.72 (1H, brs)

ESI-MS (m/e): 529 [M+H]

20

実施例 21

5-(4-ジメチルカルバモイル-フェノキシ)-6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-メタンスルホニル-フェノールを用いて、実施例 19 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.00 (3H, brs), 3.03 (3H, s), 3.08 (3H, brs), 6.81 (2H, d, $J=8.1$ Hz),

25

6. 95 (2H, d, J=8. 4Hz), 7. 26 (1/2H, brs), 7. 32 (2H, d, J=8. 1Hz), 7. 39 (1H, dd, J=7. 7, 4. 9Hz), 7. 64 (1/2H, brs), 7. 66 (1/2H, brs), 7. 79 (2H, d, J=8. 4Hz), 7. 87 (1H, ddd, J=7. 7, 7. 7, 1. 8Hz), 8. 37 (1H, d, J=7. 7Hz), 8. 63 (1H, d, J=4. 9Hz), 10. 77 (1H, brs)
 ESI-MS (m/e) : 529 [M+H]

実施例 22

10 5-(4-ジメチルカルバモイル-フェノキシ)-6-(4-メトキシ-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-メトキシフェノールを用いて、実施例19と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CDCl₃) δ : 3. 00-3. 07 (6H, m), 3. 76 (3/2H, s), 3. 77 (3/2H, s), 6. 74-6. 86 (4H, m), 6. 91 (2H, d, J=8. 4Hz), 7. 05 (1/2H, brs), 7. 19 (1/2H, brs), 7. 32-7. 36 (1H, m), 7. 35 (2H, d, J=8. 4Hz), 7. 43 (1/2H, brs), 7. 58 (1/2H, brs), 7. 83 (1H, dd, J=7. 7, 7. 7Hz), 8. 33 (1H, dd, J=7. 7, 3. 7Hz), 8. 58-8. 61 (1H, m), 10. 58 (1/2H, brs), 10. 79 (1/2H, brs)
 ESI-MS (m/e) : 481 [M+H]

実施例 23

25 5-(4-ジメチルカルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-2-イルオキシ)-1H-ベンズイミダゾール・ニトリフルオロ酢酸塩

2-ヒドロキシピリジンを用いて、実施例19と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体と

して得た。

^1H NMR (CD_3OD) δ : 6.93–7.13 (4H, m), 7.37–7.45 (2H, m), 7.41 (1Hx1/2, s), 7.56 (1Hx1/2, s), 7.64 (1Hx1/2, s), 7.67–7.75 (1H, m), 7.77–7.84 (1H, m), 7.81 (1Hx1/2, s), 8.02–8.06 (1H, m), 8.12–8.20 (1H, m), 8.27–8.33 (1H, m), 8.82–8.87 (1H, m)

ESI-MS (m/e): 452 [M+H]

10 実施例 24

5-(4-ジメチルカルバモイル-フェノキシ)-6-(2-エトキシカルボニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-ヒドロキシ安息香酸 エチルエステルを用いて、実施例 19 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 1.20 (3H, t, $J=7.0\text{ Hz}$), 3.01 (3H, brs), 3.07 (3H, brs), 4.17 (2H, q, $J=7.0\text{ Hz}$), 6.80–6.91 (3H, m), 7.08–7.14 (1H, m), 7.12 (1/2H, brs), 7.18 (1/2H, brs), 7.26–7.41 (4H, m), 7.49 (1/2H, brs), 7.61 (1/2H, brs), 7.84–7.87 (2H, m), 8.34–8.38 (1H, m), 8.61–8.62 (1H, m), 10.85 (1/2H, brs), 10.95 (1/2H, brs)

ESI-MS (m/e): 523 [M+H]

25

実施例 25

5-(2-ジメチルカルバモイル-フェノキシ)-6-(4-ジメチルカルバモイル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-ヒドロキシ安息香酸 ジメチルアミドを用いて、実施例 19 と同様の方

法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 2.64–3.08 (12H, m), 6.81 (1/2H, s), 6.85 (1/2H, s), 6.94 (1H, dd, $J=$
5 8.8, 2.7 Hz), 7.08 (1/2H, s), 7.12 (1/2H, s), 7.21 (1/2H, s), 7.24 (1/2H, s), 7.25–7.29 (2H, m), 7.30–7.34 (1H, m), 7.35–7.53 (2H, m), 7.59 (1H, d, $J=3.1$ Hz), 7.83–7.88 (1H, m), 8.33–8.38 (1H, m), 8.63 (1H, d, $J=$
10 4.9 Hz), 10.52 (1H, brs)
ESI-MS (m/e): 522 [$M+H$]

実施例 26

5 – (2-アセチルフェノキシ) – 6 – (4-ジメチルカルバモイルフェ
15 ノキシ) – 2-ピリジン – 2-イル – 1H-ベンズイミダゾール

2-アセチルフェノールを用いて、実施例 19 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 2.36 (3/2H, s), 2.40 (3/2H, s), 3.00 (3H, brs), 3.08 (3H, brs), 6.76–6.
20 84 (3H, m), 7.05–7.11 (1H, m), 7.15–7.25 (1H, m), 7.26–7.28 (1H, m), 7.32–7.35 (2H, m), 7.38–7.42 (1H, m), 7.63 (1/2H, s), 7.68 (1/2H, s), 7.78 (1H, d, $J=7.4$ Hz), 7.86–7.90 (1H, m), 8.39 (1H, d, $J=7.0$ Hz), 8.65 (1H,
25 s), 10.73 (1H x 1/2, brs), 10.88 (1H x 1/2, brs)
ESI-MS (m/e): 493 [$M+H$]

実施例 27

5-(4-アセチルフェノキシ)-6-(4-ジメチルカルバモイルフェ
ノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-アセチルフェノールを用いて、実施例19と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- 5 $^1\text{H NMR}$ (CDCl_3) δ : 2.55 (3H, s), 2.98 (3H, br s), 3.09 (3H, br s), 6.70-6.90 (4H, m), 7.23 (1/2H, s), 7.34 (1/2H, s), 7.26 (1/2H, s), 7.33-7.35 (2H, m), 7.38-7.42 (1H, m), 7.65 (1/2H, s), 7.68 (1/2H, s) 7.86-7.91 (3H, m), 8.40 (1H, d, $J=7.8\text{ Hz}$), 8.65 (1H, d, $J=3.5\text{ Hz}$), 10.85 (1/2H, br s), 10.95 (1/2H, br s)

ESI-MS (m/e): 493 $[\text{M}+\text{H}]$

15 実施例28

5-(2-シアノフェノキシ)-2-ピリジン-2-イル-6-(4-シア
ノフェノキシ)-1H-ベンズイミダゾール

- 2-ヒドロキシベンゾニトリル、及び4-ヒドロキシベンゾニトリルを
順次用いて、実施例1と同様の方法、これに準じた方法又はこれらと常法とを
20 組み合わせることにより、表題化合物を無色固体として得た。

- $^1\text{H NMR}$ (CDCl_3) δ : 6.80 (1H, t, $J=8.8\text{ Hz}$), 6.86 (1H, d, $J=8.8\text{ Hz}$), 6.89 (1H, d, $J=8.8\text{ Hz}$), 7.08 (1H, td, $J=7.6\text{ Hz}$, 7.4 Hz), 7.34-7.47 (3H, m), 7.47-7.58 (3H, m), 7.67 (1H, d, $J=5.2\text{ Hz}$), 7.88 (1H, t, $J=7.6\text{ Hz}$), 8.38 (1H, d, $J=7.6\text{ Hz}$), 8.65 (1H, d, $J=4.0\text{ Hz}$), 10.58 (1H, br s)

ESI-MS (m/e): 430 $[\text{M}+\text{H}]$

実施例 29

5 - (2-シアノフェノキシ) - 2-ピリジン-2-イル-6 - (3-シアノフェノキシ) - 1H-ベンズイミダゾール

実施例 28 で得られた 4-フルオロ-5 - (2-シアノフェノキシ) -
5 2-ニトロフェニルアミン、及び 3-ヒドロキシベンゾニトリルを用いて、
実施例 28 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ
ることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 6.93-6.84 (1H, m), 6.96-7.
12 (3H, m), 7.27-7.38 (3H, m), 7.38-7.48
10 (2H, m), 7.54 (1H, dd, $J=1.6\text{ Hz}$, 7.6 Hz), 7.
68 (1H, d, $J=13.2\text{ Hz}$), 7.89 (1H, t, $J=7.6\text{ Hz}$),
8.42 (1H, d, $J=7.6\text{ Hz}$), 8.65 (1H, s)
ESI-MS (m/e): 430 [$\text{M}+\text{H}$]

15 実施例 30

5 - (2-シアノフェノキシ) - 2-ピリジン-2-イル-6 - (4 -
(2-ヒドロキシエチル) - フェノキシ) - 1H-ベンズイミダゾール・トリ
フルオロ酢酸塩

4-ヒドロキシエチルフェノールを用いて、実施例 29 と同様の方法、こ
20 れに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を
褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 2.78 (2H, t, $J=7.0\text{ Hz}$), 3.7
2 (2H, t, $J=7.0\text{ Hz}$), 6.83 (2H, d, $J=8.6\text{ Hz}$),
6.94 (1H, d, $J=8.6\text{ Hz}$), 7.19-7.21 (3H, m),
25 7.41 (1H, s), 7.56 (1H, t, $J=8.6\text{ Hz}$), 7.63-
7.73 (3H, m), 8.11 (1H, t, $J=7.8\text{ Hz}$), 8.26
(1H, d, $J=7.8\text{ Hz}$), 8.85 (1H, d, $J=4.7\text{ Hz}$)
ESI-MS (m/e): 449 [$\text{M}+\text{H}$]

実施例 3 1

5-(4-シアノフェノキシ)-2-ピリジン-2-イル-6-(1-オキシ-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

1-オキシ-ピリジン-3-オール、及び4-シアノフェノールを順次用
 5 いて、実施例1と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl₃) δ : 6.86-6.90 (2H, m), 7.11 (1/2H, ddd, $J=7.3, 2.8, 1.5\text{ Hz}$), 7.13 (1/2H, ddd, $J=7.3, 2.8, 1.5\text{ Hz}$), 7.18 (1/2H, dd, $J=7.3, 4.8\text{ Hz}$), 7.20 (1/2H, dd, $J=7.3, 4.8\text{ Hz}$), 7.36-7.41 (1H, m), 7.37 (1/2H, s), 7.44 (1/2H, s), 7.48-7.57 (3H, m), 7.60 (1/2H, s), 7.66 (1/2H, s), 8.20 (1/2H, d, $J=2.8\text{ Hz}$), 8.21 (1/2H, d, $J=2.8\text{ Hz}$), 8.30 (1/2H, d, $J=4.8, 1.5\text{ Hz}$), 8.32 (1/2H, dd, $J=4.8, 1.5\text{ Hz}$), 8.37 (1H, d, $J=7.0\text{ Hz}$), 8.65-8.70 (1H, m)

ESI-MS (m/e): 422 [M+H]

20 実施例 3 2

2-ピラジン-2-イル-5, 6-ビス(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

実施例1(工程3)で得られた4, 5-ビス-(ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン15mgのピリジン1ml溶液に、ピラジン-2-カルボン酸7.7mg、及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・一塩酸塩20mgを加え、反応液を室温にて一終夜攪拌した。反応液を、酢酸エチルにて希釈し、飽和重曹水、水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をオキシ塩化リン1mlに懸濁させ、反応液を100度にて一終夜攪拌し

た。オキシ塩化リンを減圧留去した後、酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、残渣を分取用薄層クロマトグラフィー (Kieselgel™ 60 F₂₅₄、Art 5744 (メルク社製)、クロロホルム/メタノール=15/1+0、

5 1%アンモニア水) にて精製し、表題化合物を黄色固体として得た。

¹H NMR (CD₃OD) δ: 7.20–7.82 (6H, m), 8.11 (2H, s), 8.20–8.28 (2H, m), 8.67 (1H, s), 8.75 (1H, s), 9.47 (1H, s)

ESI-MS (m/e): 383 [M+H]

10

実施例 33

5-(4-メタンスルホニルフェノキシ)-2-ピラジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 9 で得られた 4-(4-メタンスルホニルフェノキシ)-5-(ピ
15 リジン-3-イルオキシ)-ベンゼン-1, 2-ジアミンを用いて、実施例 3
2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CDCl₃) δ: 2.91 (3H, s), 3.04 (3H, d, J=1.6 Hz), 6.96 (2H, d, J=9.0 Hz), 7.14–7.18 (1H, m),
20 7.19–7.25 (1H, m), 7.35 (1/2H, s), 7.41 (1/2H, s), 7.68 (1/2H, s), 7.73 (1/2H, s), 7.84 (2H, dd, J=9.0, 1.6 Hz), 8.24 (1H, dd, J=7.1, 2.7 Hz), 8.32–8.35 (1H, m), 8.59–8.62 (1H, m), 8.69 (1H, d, J=2.5 Hz),
25 9.63–9.64 (1H, m), 10.91 (1H x 1/2, br s), 10.8 (1H x 1/2, br s)

ESI-MS (m/e): 460 [M+H]

実施例 34

5- (4-ジメチルカルバモイル-フェノキシ) -6- (2-メタンスルホニル-フェノキシ) -2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例20で得られた4- (4-ジメチルカルバモイル-フェノキシ) -5- (2-メタンスルホニル-フェノキシ) -ベンゼン-1, 2-ジアミンを用いて、実施例32と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.95 (3/2H, s), 2.99 (3H, brs), 3.05 (3/2H, brs), 3.08 (3H, brs), 6.80-6.91 (3H, m), 6.89-6.95 (3H, s), 7.17-7.24 (1H, m), 7.20 (1/2H, s), 7.35-7.39 (2H, m), 7.35-7.39 (1/2H, m), 7.46-7.54 (1H, m), 7.66 (1/2H, s), 7.70 (1/2H, s), 8.02 (1H, d, $J=7.8\text{ Hz}$), 8.60 (1H, d, $J=2.4\text{ Hz}$), 8.67 (1H, dd, $J=2.4, 2.0\text{ Hz}$), 9.61 (1H, d, $J=2.0\text{ Hz}$), 10.65 (1/2H, brs), 10.74 (1/2H, brs)

ESI-MS (m/e): 530 $[\text{M}+\text{H}]$

実施例35

5- (2-シアノ-フェノキシ) -2-ピラジン-2-イル-6- (4-メタンスルホニル-フェノキシ) -1H-ベンズイミダゾール

実施例17で得られた4- (2-シアノ-フェノキシ) -5- (4-メタンスルホニル-フェノキシ) -ベンゼン-1, 2-ジアミンを用いて、実施例32と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.09 (3H, s), 6.91 (1H, d, $J=7.8\text{ Hz}$), 6.96-7.00 (2H, m), 7.15 (1H, td, $J=7.6\text{ Hz}, 1.0\text{ Hz}$), 7.54-7.58 (1H, m), 7.64 (1H, dd, $J=1.6\text{ Hz}, 7.8\text{ Hz}$), 7.72 (2H, d, $J=3.0\text{ Hz}$)

5 Hz), 7.87 (2H, d, J=8.6 Hz), 8.77 (1H, d, J=2.7 Hz), 8.81-8.85 (1H, dd, J=1.6 Hz, 2.7 Hz), 8.52 (1H, d, J=1.6 Hz)

ESI-MS (m/e) : 484 [M+H]

5

実施例 36

5-(2-メトキシフェノキシ)-6-(4-メタンスルホニルフェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例 16 で得られた 4-(2-メトキシフェノキシ)-5-(4-メタ
10 ンスルホニルフェノキシ)-ベンゼン-1,2-ジアミンを用いて、実施例
32 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を得た。

¹H NMR (CDCl₃) δ : 3.04 (3H, s), 3.71 (3H, d, J
=3.1 Hz), 6.86-6.97 (3H, m), 7.00 (1/2H,
15 s), 7.06-7.14 (3H, m), 7.34 (1/2H, s), 7.3
6 (1/2H, s), 7.68 (1/2H, s), 7.85 (2H, dd, J
=9.0, 3.1 Hz), 8.56-8.59 (1H, m), 8.65 (1H,
dd, J=4.3, 2.7 Hz), 9.57-9.61 (1H, m), 10.
24 (1H x 1/2, brs), 10.34 (1H x 1/2, brs)

20 ESI-MS (m/e) : 489 [M+H]

実施例 37

5-(4-ジメチルカルバモイルフェノキシ)-6-(2-メタンスルホニ
ルフェノキシ)-2-チアゾール-2-イル-1H-ベンズイミダゾール

25 実施例 20 で得られた 4-(4-ジメチルカルバモイルフェノキシ)-
5-(2-メタンスルホニルフェノキシ)-ベンゼン-1,2-ジアミン、
及びチアゾール-2-カルボキサアルデヒドを用いて、実施例 1 (工程 4) と
同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
表題化合物を得た。

^1H NMR (CDCl_3) δ : 2.94 (3/2H, s), 2.96 (3H, brs), 3.05 (3/2H, brs), 3.08 (3H, brs), 6.87-6.93 (3H, m), 7.13 (1/2H, brs), 7.16-7.23 (1H, m), 7.34-7.38 (2H, m), 7.45-7.53 (1H, m), 7.51 (1/2H, brs), 7.54-7.56 (1H, m), 7.62 (1/2H, s), 7.66 (1/2H, s), 7.94 (1H, d, $J=3.1\text{ Hz}$), 8.01 (1H, dd, $J=7.8, 1.6\text{ Hz}$)

ESI-MS (m/e): 535 $[\text{M}+\text{H}]$

10

実施例 38

5-(2-シアノフェノキシ)-2-ピリダジン-3-イル-6-(4-メタン
スルホニルフェノキシ)-1H-ベンズイミダゾール

実施例 17 で得られた 4-(2-シアノフェノキシ)-5-(4-メタン
15 スルホニルフェノキシ)-ベンゼン-1, 2-ジアミン 15 mg の N-メチル
ピロリドン 0.3 ml 溶液に、ピリダジン-3-カルボン酸 3.3 mg、
1-ヒドロキシベンゾトリアゾール 15 mg、及び 1-(3-ジメチルアミ
ノプロピル)-3-エチルカルボジイミド・一塩酸塩 15 mg を順次加え、反
応液を室温にて一終夜攪拌した。反応液を、酢酸エチルにて希釈し、飽和重曹
20 水にて洗浄後、溶媒を減圧留去した。得られた残渣を N-メチルピロリドン 0.
2 ml に溶解し、三トリフルオロメタンスルホン酸イッテリビウム 5 mg を加
え、反応液を 140 度にて一終夜攪拌した。反応混合物を、逆相中圧液体クロ
マトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-ア
セトニトリル-0.1% トリフルオロ酢酸] にて精製した。得られたフラク
25 ションの溶媒を減圧留去することにより、表題化合物を褐色固体として得た。

^1H NMR (CD_3OD) δ : 3.10 (3H, s), 6.92 (1H, d, $J=7.6\text{ Hz}$), 6.99 (2H, d, $J=8.6\text{ Hz}$), 7.20 (1H, t, $J=7.6\text{ Hz}$), 7.58 (1H, t, $J=7.6\text{ Hz}$), 7.64 (1H, d, $J=7.6\text{ Hz}$), 7.70-7.80 (2H, m), 7.87 (

2H, d, $J=8.6\text{ Hz}$), 7.96–8.02 (1H, m), 8.58 (1H, brs), 9.36 (1H, brs)

ESI-MS (m/e): 484 [M+H]

5 実施例 39

5-(2-シアノフェノキシ)-2-[1, 2, 5]-チアジアゾール-3-イル-6-(4-メタンスルホニルフェノキシ)-1H-ベンズイミダゾール

10 [1, 2, 5]-チアジアゾール-3-カルボン酸を用いて、実施例 38 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.09 (3H, s), 6.90 (1H, d, $J=7.8\text{ Hz}$), 6.98 (2H, d, $J=8.6\text{ Hz}$), 7.19 (1H, t, $J=7.7\text{ Hz}$), 7.56 (1H, t, $J=7.8\text{ Hz}$), 7.64
15 (1H, d, $J=7.8\text{ Hz}$), 7.72 (1H, s), 7.73 (1H, s), 7.87 (2H, d, $J=8.6\text{ Hz}$), 9.39 (1H, s)

ESI-MS (m/e): 490 [M+H]

実施例 40

20 5-(2-シアノフェノキシ)-2-(2H-[1, 2, 3]-トリアゾール-4-イル)-6-(4-メタンスルホニルフェノキシ)-1H-ベンズイミダゾール

25 2H-[1, 2, 3]-トリアゾール-4-カルボン酸を用いて、実施例 38 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.12 (3H, s), 6.91 (1H, d, $J=7.6\text{ Hz}$), 6.98 (2H, d, $J=8.6\text{ Hz}$), 7.20 (1H, t, $J=7.6\text{ Hz}$), 7.56 (1H, t, $J=7.6\text{ Hz}$), 7.64 (1H, d, $J=7.6\text{ Hz}$), 7.70 (1H, d, $J=2.7\text{ Hz}$), 7.

8.7 (2H, d, $J=8.6$ Hz), 8.52 (1H, brs)

ESI-MS (m/e): 473 [M+H]

実施例 4 1

5 5-(2-シアノフェノキシ)-2-フラザン-3-イル-6-(4-メタ
ンスルホニルフェノキシ)-1H-ベンズイミダゾール

フラザン-3-カルボン酸を用いて、実施例 3 8 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

10 ^1H NMR (CD_3OD) δ : 3.06 (3H, s), 6.84 (1H, d, $J=7.8$ Hz), 6.92 (2H, d, $J=8.6$ Hz), 7.15 (1H, t, $J=7.8$ Hz), 7.52 (1H, t, $J=7.8$ Hz), 7.57-7.62 (2H, m), 7.82 (2H, d, $J=8.6$ Hz)

ESI-MS (m/e): 474 [M+H]

15

実施例 4 2

5-(2-シアノフェノキシ)-2-(4H-[1, 2, 4]-トリアゾール-3-イル)-6-(4-メタンスルホニルフェノキシ)-1H-ベンズイミダゾール

20 [1, 2, 4]-トリアゾール-3-カルボン酸を用いて、実施例 3 8 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CD_3OD) δ : 3.07 (3H, s), 6.92 (1H, d, $J=7.8$ Hz), 6.98 (2H, d, $J=8.6$ Hz), 7.19 (1H, t, $J=7.8$ Hz), 7.55 (1H, t, $J=7.8$ Hz), 7.63 (1H, d, $J=7.8$ Hz), 7.74 (2H, d, $J=6.3$ Hz), 7.85 (2H, d, $J=8.6$ Hz), 8.73 (1H, s)

25

ESI-MS (m/e): 473 [M+H]

実施例 4 3

5 - (2 - カルバモイル - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (ピ
リジン - 3 - イルオキシ) - 1H - ベンズイミダゾール

実施例 5 で得られた 5 - (2 - シアノ - フェノキシ) - 2 - ピリジン - 2 -
5 イル - 6 - (ピリジン - 3 - イルオキシ) - 1H - ベンズイミダゾール 3. 5
mg の 80 % 硫酸溶液を、反応液を 50 度にて終夜攪拌した。反応混合物を、
逆相中圧液体クロマトグラフィー [ODS - AS - 360 - CC (YMC 社製)
) 移動相 : 水 - アセトニトリル - 0. 1 % トリフルオロ酢酸] にて精製し、得
られたフラクションの溶媒を減圧留去することにより、表題化合物を無色固体
10 として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 5. 59 (1H, brs), 6. 80 (1H, d
d, $J=8. 4\text{ Hz}$, $0. 8\text{ Hz}$), 7. 01 - 7. 48 (7H, m), 7.
88 (1H, td, $J=8. 0\text{ Hz}$, $2. 0\text{ Hz}$), 8. 16 (1H, dd,
 $J=8. 4\text{ Hz}$, $2. 0\text{ Hz}$), 8. 21 (1H, s), 8. 27 - 8. 85
15 (1H, m), 8. 38 (1H, d, $J=8. 0\text{ Hz}$), 8. 63 (1H, d,
 $J=8. 4\text{ Hz}$)

ESI-MS (m/e) : 424 [$M+H$]

実施例 4 4

20 5 - (4 - カルバモイル - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (ピ
リジン - 3 - イルオキシ) - 1H - ベンズイミダゾール

実施例 7 で得られた 5 - (4 - シアノ - フェノキシ) - 2 - ピリジン - 2 -
イル - 6 - (ピリジン - 3 - イルオキシ) - 1H - ベンズイミダゾールを用い
て、実施例 4 3 と同様の方法、これに準じた方法又はこれらと常法とを組み合
25 わせることにより、表題化合物を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 6. 82 (2H, d, $J=8. 8\text{ Hz}$), 7. 1
3 (1H, ddd, $J=8. 4$, $2. 6$, $1. 5\text{ Hz}$), 7. 17 (1H, d
d, $J=8. 4$, $4. 8\text{ Hz}$), 7. 13 - 7. 20 (1H, m), 7. 3
0 - 7. 37 (1H, m), 7. 38 (1H, ddd, $J=7. 7$, $4. 4$,

1. 1 Hz), 7. 71 (2H, d, J=8. 8 Hz), 7. 87 (1H, d
dd, J=7. 7, 7. 7, 1. 8 Hz), 8. 16 (1H, dd, J=2.
6, 0. 7 Hz), 8. 25 (1H, dd, J=4. 8, 1. 5 Hz), 8.
39 (1H, ddd, J=7. 7, 1. 1, 0. 7 Hz), 8. 61 (1H,
5 ddd, J=4. 4, 1. 8, 0. 7 Hz)
ESI-MS (m/e) : 424 [M+H]

実施例 45

5 5-(4-カルバモイル-フェノキシ)-6-(ピリジン-3-イルオキ
シ)-2-チアゾール-2-イル-1H-ベンズイミダゾール
10

実施例 7 で得られた 4-(4, 5-ジアミノ-2-(ピリジン-3-イルオ
キシ)-フェノキシ)-ベンゾニトリルを用いて、実施例 37、及び実施例 4
3 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を得た。

15 ¹H NMR (CDCl₃) δ : 6. 01 (2H, brs), 6. 82-6. 86
(2H, m), 7. 13 (1H, ddd, J=8. 4, 2. 9, 1. 5 Hz),
7. 18 (1H, dd, J=8. 4, 4. 6 Hz), 7. 29 (1/2H,
s), 7. 30 (1/2H, s), 7. 52-7. 54 (1H, m), 7. 9
2 (2H, d, J=8. 8 Hz), 7. 61 (1/2H, s), 7. 64 (1
20 /2H, s), 7. 70-7. 75 (2H, m), 7. 92 (1H, d, J=
2. 9 Hz), 8. 21 (1H, d, J=2. 9 Hz), 8. 29 (1H, d
d, J=4. 6, 1. 5 Hz)
ESI-MS (m/e) : 430 [M+H]

25 実施例 46

5-(4-カルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(
2-カルバモイル-フェノキシ)-1H-ベンズイミダゾール

実施例 28 で得られた 5-(2-シアノ-フェノキシ)-2-ピリジン-2
-イル-6-(4-シアノ-フェノキシ)-1H-ベンズイミダゾールを用い

て、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CD_3OD) δ : 7.86 (2H, d, $J=8.8\text{ Hz}$), 7.13 (1H, t, $J=7.6\text{ Hz}$), 7.39 (1H, t, $J=7.6\text{ Hz}$),
 5 7.45–7.74 (4H, m), 7.78 (2H, d, $J=8.8\text{ Hz}$),
 7.91 (1H, d, $J=7.6\text{ Hz}$), 7.99 (1H, t, $J=7.6\text{ Hz}$),
 8.30 (1H, d, $J=7.6\text{ Hz}$), 8.74 (1H, s)
 ESI-MS (m/e) : 466 [$M+H$]

10 実施例 47

5-(3-カルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(2-カルバモイル-フェノキシ)-1H-ベンズイミダゾール・トリフルオロ酢酸塩

実施例 29 で得られた 5-(2-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(3-シアノ-フェノキシ)-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CD_3OD) δ : 6.78–6.96 (1H, m), 6.96–7.08 (1H, m), 7.08–7.20 (1H, m), 7.30–7.70 (7H, m), 7.88–8.08 (2H, m), 8.29 (1H, d, $J=7.6\text{ Hz}$), 8.73 (1H, s)
 20 ESI-MS (m/e) : 466 [$M+H$]

実施例 48

25 5-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-6-(2-カルバモイル-フェノキシ)-1H-ベンズイミダゾール

実施例 17 で得られた 5-(2-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法

とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.12 (3H, s), 6.85 (1H, d, $J=7.8\text{ Hz}$), 6.98 (2H, d, $J=8.6\text{ Hz}$), 7.15 (1H, t, $J=7.8\text{ Hz}$), 7.42 (1H, t, $J=7.8\text{ Hz}$), 7.52 (1H, dd, $J=4.3\text{ Hz}$, 7.0 Hz), 7.64 (2H, brs), 7.83 (2H, d, $J=8.6\text{ Hz}$), 7.91 (1H, d, $J=7.8\text{ Hz}$), 8.01 (1H, dd, $J=7.0\text{ Hz}$, 7.8 Hz), 8.32 (1H, d, $J=7.8\text{ Hz}$), 8.76 (1H, d, $J=4.3\text{ Hz}$)
ESI-MS (m/e): 501 [M+H]

10

実施例 49

5-(4-メタンスルホニルフェノキシ)-2-ピラジン-2-イル-6-(2-カルバモイルフェノキシ)-1H-ベンズイミダゾール

実施例 35 で得られた 5-(2-シアノフェノキシ)-2-ピラジン-2-イル-6-(4-メタンスルホニルフェノキシ)-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.05 (3H, s), 5.80 (1H, brs), 6.82 (1H, d, $J=7.8\text{ Hz}$), 6.95-7.00 (3H, m), 7.17 (2H, q, $J=8.2\text{ Hz}$), 7.36-7.39 (2H, m), 7.76 (1H, d, $J=7.8\text{ Hz}$), 7.81-7.85 (2H, m), 8.15 (1H, d, $J=7.8\text{ Hz}$), 8.63 (1H, s), 8.72 (1H, s), 9.66 (1H, s), 10.80 (1H, brs)
ESI-MS (m/e): 502 [M+H]

25

実施例 50

5-(4-カルバモイルフェノキシ)-2-ピリジン-2-イル-6-(1-オキシピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 31 で得られた 5-(4-シアノフェノキシ)-2-ピリジン-

2-イル-6-(1-オキシ-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例43と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CDCl₃) δ: 6.82-6.86 (2H, m), 7.15-7.26 (2H, m), 7.38-7.42 (1H, m), 7.41 (1/2H, s), 7.44 (1/2H, s), 7.54-7.58 (1H, m), 7.62 (1/2H, s), 7.65 (1/2H, s), 7.71-7.75 (2H, m), 8.12-8.16 (1H, m), 8.22-8.27 (1H, m), 8.37 (1H, d, J=7.0 Hz), 8.64-8.67 (1H, m),
ESI-MS (m/e): 440 [M+H]

実施例51

5-(3-カルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例6で得られた5-(3-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例43と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CDCl₃) δ: 7.07 (1H, ddd, J=0.8, 3.4, 10.3 Hz), 7.36 (1H, dd, J=1.9, 3.4 Hz), 7.40 (1H, t, J=10.3 Hz), 7.56 (1H, s), 7.57-7.62 (2H, m), 7.69 (1H, dd, J=7.2, 10.3 Hz), 7.73 (1H, s), 7.78 (1H, ddd, J=0.8, 3.8, 11.4 Hz), 8.16 (1H, dt, J=3.0, 11.0 Hz), 8.29 (1H, dt, J=0.4, 11.0 Hz), 8.37-8.41 (2H, m), 8.80 (1H, dt, J=0.4, 3.8 Hz)

ESI-MS (m/e): 424 [M+H]⁺

実施例52

5 - (2-カルバモイル-フェノキシ) - 6 - (4-ジメチルカルバモイル-フェノキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 28 で得られた 4-フルオロ-5-(2-シアノ-フェノキシ)-2-ニトロ-フェニルアミン、及び 4-ヒドロキシ安息香酸 ジメチルアミド
5 を用いて、実施例 1 及び実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.98 (3H, brs), 3.07 (3H, brs), 5.72 (1H, brs), 6.76-6.83 (3H, m), 6.97 (1/2H, brs), 7.09 (1/2H, dd, $J=7.7, 7.7$
10 Hz), 7.11 (1/2H, dd, $J=7.7, 7.7$ Hz), 7.14 (1/2H, s), 7.30-7.35 (3H, m), 7.37-7.40 (1H, m), 7.67 (1H, d, $J=7.7$ Hz), 7.86 (1H, dd, $J=7.7, 7.7, 1.5$ Hz), 8.12 (1H, dd, $J=7.7, 1.8$ Hz), 8.14 (1H, dd, $J=7.7, 1.8$ Hz), 8.
15 38 (1H, d, $J=7.7$ Hz), 8.61-8.62 (1H, m), 10.99 (1H, brs)

ESI-MS (m/e): 494 $[\text{M}+\text{H}]$

実施例 53

20 5 - (2-カルバモイル-フェノキシ) - 6 - (4-ジメチルカルバモイル-フェノキシ) - 2-チアゾール-2-イル-1H-ベンズイミダゾール

実施例 52 で得られた 4-(2-シアノ-フェノキシ)-5-ビス-(4-ジメチルカルバモイル-フェノキシ)-ベンゼン-1,2-ジアミンを用いて、
実施例 37 及び実施例 43 と同様の方法、これに準じた方法又はこれらと常法
25 とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.97 (3H, brs), 3.08 (3H, brs), 5.91 (1/2H, brs), 6.00 (1/2H, brs), 6.75-6.82 (3H, m), 6.93 (1/2H, brs), 7.07-7.13 (1H, m), 7.17 (1H, brs), 7.25 (1/2H, br

s), 7.32 (2H, d, J=8.8 Hz), 7.53 (1H, d, J=2.9 Hz), 7.65 (2H, d, J=8.8 Hz), 7.37-7.40 (1H, m), 7.65 (1H, d, J=7.0 Hz), 7.92-7.93 (1H, m), 8.11 (1/2H, d, J=6.6 Hz), 8.13 (1/2H, d, J=6.6 Hz)

ESI-MS (m/e) : 500 [M+H]

実施例 54

5- (2-カルバモイル-フェノキシ) -2-ピリジン-2-イル-6- (4- (2- (2, 2, 2-トリフルオロ-アセトキシ) -エチル) -フェノキシ) -1H-ベンズイミダゾール・トリフルオロ酢酸塩

実施例 30 で得られた 5- (2-シアノ-フェノキシ) -2-ピリジン-2-イル-6- (4- (2-ヒドロキシエチル) -フェノキシ) -1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はそれらと常法とを組み合わせ、反応混合物を逆相中圧液体クロマトグラフィー (ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸) にて精製し、得られたフラクションの溶媒を減圧除去することにより、表題化合物を無色固体として得た。

¹H NMR (CD₃OD) δ: 2.94 (2H, t, J=6.7 Hz), 4.17 (2H, t, J=6.7 Hz), 6.84 (2H, d, J=8.6 Hz), 6.90 (1H, d, J=8.6 Hz), 7.19 (1H, d, J=8.6 Hz), 7.25 (1H, d, J=8.6 Hz), 7.41 (1H, s), 7.42-7.48 (1H, m), 7.58 (1H, s), 7.61-7.63 (1H, m), 8.09 (1H, t, J=7.8 Hz), 8.25 (1H, t, J=7.8 Hz), 8.83 (1H, d, J=4.7 Hz)

ESI-MS (m/e) : 563 [M+H]

実施例 55

5- (4-カルバモイル-フェノキシ) -6- (4-ジメチルカルバモイ

フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール

実施例 18 で得られた 4 - フルオロ - 5 - (4 - ジメチルカルバモイル - フェノキシ) - 2 - ニトロ - フェニルアミン、及び 4 - ヒドロキシ - ベンゾニ
 トリルを用いて、実施例 1 及び実施例 43 と同様の方法、これに準じた方法又
 5 はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.97 (3H, brs), 3.08 (3H, brs), 6.80 - 6.86 (4H, m), 7.26 - 7.29 (2H, m),
 7.31 (1/2H, s), 7.35 (1/2H, s), 7.38 - 7.41 (1H, m), 7.66 - 7.70 (3H, m), 7.86 - 7.91 (1H,
 10 m), 8.40 (1H, d, $J=7.8\text{ Hz}$), 8.65 (1H, d, $J=4.7\text{ Hz}$), 10.89 (1H, brs)
 ESI-MS (m/e): 494 [M+H]

実施例 56

15 5 - (4 - メチルカルバモイル - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダゾール

実施例 10 で得られた 5 - (4 - メトキシカルボニル - 2 - ピリジン - 2 - イル - 6 - (ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダゾール 3.0
 mg のメタノール 1 ml 溶液に、40% メチルアミンメタノール溶液 0.05
 20 ml を加え、反応液を室温にて一終夜攪拌した。溶媒を減圧留去した後、分取
 用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール = 20/1) にて精製し、表題化
 合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.96 (3/2H, s), 2.97 (3/2H,
 25 s), 6.80 (1H, d, $J=8.4\text{ Hz}$), 7.14 - 7.23 (2H, m), 7.36 (1H, brs), 7.40 (1H, dd, $J=7.7, 4.7\text{ Hz}$), 7.62 (1H, brs), 7.66 (2H, d, $J=8.4\text{ Hz}$), 7.90 (1H, dd, $J=7.7, 7.7\text{ Hz}$), 8.10 (1H, brs), 8.20 (1H, brs), 8.37 (1H, d, $J=7.7\text{ Hz}$)

z), 8.63 (1H, d, J=4.7 Hz)

ESI-MS (m/e) : 438 [M+H]

実施例 57

5 5-(4-メタンスルホニルフェノキシ)-6-(2-メチルカルバモイルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 14 で得られた 5-(2-エトキシカルボニルフェノキシ)-6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾールを用いて、実施例 56 と同様の方法、これに準じた方法又は
10 これらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CDCl₃) δ : 2.73 (3/2H, s), 2.74 (3/2H, s), 3.03 (3H, s), 6.74-6.79 (1H, m), 6.89-7.6.96 (2H, m), 7.01 (1/2H, brs), 7.09-7.15 (1H, m), 7.17 (1/2H, brs), 7.30 (1/2H, brs),
15 s), 7.40 (1/2H, brs), 7.40-7.44 (1H, m), 7.72 (1H, s), 7.82 (2H, dd, J=8.2, 6.7 Hz), 7.88-7.93 (1H, m), 8.10-8.15 (1H, m), 8.41 (1H, d, J=6.8 Hz), 8.66 (1H, s), 11.09 (1/2H, brs), 11.12 (1/2H, brs)

20 ESI-MS (m/e) : 515 [M+H]

実施例 58

5-(4-ジメチルカルバモイルフェノキシ)-6-(2-メチルカルバモイルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

25 実施例 24 で得られた 5-(2-エトキシカルボニルフェノキシ)-6-(4-ジメチルカルバモイルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾールを用いて、実施例 56 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CDCl₃) δ : 2.77 (3H, d, J=3.5 Hz), 2.9

9 (3H, brs), 3.08 (3H, brs), 6.75–6.86 (3H, m), 7.00–7.14 (1H, m), 7.15–7.27 (1/2H, m), 7.27–7.32 (2H, m), 7.27–7.32 (1/2H, m), 7.35–7.42 (2H, m), 7.69 (1H, s), 7.87–7.91 (1H, m), 8.11–8.17 (1H, m), 8.40 (1H, d, $J=7.4\text{ Hz}$), 8.66 (1H, s), 11.01 (1H, brs)
 5 ESI-MS (m/e): 508 [M+H]

実施例 59

10 5-(2-メチルカルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 1 (工程 2) で得られた 3-(2-フルオロ-4-ニトロ-フェノキシ)-ピリジン、及び 2-ヒドロキシ安息香酸 エチルエステルを用いて、実施例 1 及び実施例 56 と同様の方法、これに準じた方法又はこれらと常法とを
 15 組み合わせることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.70–8.80 (3H, m), 6.77 (1H, d, $J=7.6\text{ Hz}$), 7.25–7.44 (7H, m), 7.67 (1H, s), 7.82 (1H, t, $J=7.6\text{ Hz}$), 8.15 (1H, t, $J=7.6\text{ Hz}$), 8.18–8.26 (1H, m), 8.26–8.36 (1H, m), 8.38 (1H, d, $J=7.6\text{ Hz}$), 8.64 (1H, d, $J=2.4\text{ Hz}$), 10.6 (1H, brs)
 20

ESI-MS (m/e): 438 [M+H]

実施例 60

25 5-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-6-(2-(2H-テトラゾール-5-イル)-フェノキシ)-1H-ベンズイミダゾール・トリフルオロ酢酸塩

実施例 17 で得られた 5-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-6-(2-シアノ-フェノキシ)-1H-ベンズイミダゾール

ール 30 mg のジメチルホルムアミド 1 ml 溶液に、アジ化ナトリウム 30 mg、及び塩化マグネシウム 32 mg を加え、反応液を 170 度にて 24 時間攪拌した。反応混合物を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションの溶媒を減圧留去し、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.11 (3H, s), 6.75 (2H, d, $J=8.6\text{ Hz}$), 6.96 (1H, d, $J=7.6\text{ Hz}$), 7.29 (1H, t, $J=7.6\text{ Hz}$), 7.51 (1H, t, $J=7.6\text{ Hz}$), 7.62 (2H, d, $J=8.6\text{ Hz}$), 7.58-7.69 (1H, m), 7.73 (1H, s), 7.93 (1H, s), 8.13 (1H, d, $J=7.6\text{ Hz}$), 8.08-8.16 (1H, m), 8.33-8.38 (1H, m), 8.84-8.88 (1H, m)

ESI-MS (m/e): 526 [M+H]

15

実施例 61

5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-(2-(2-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-1H-ベンズイミダゾール

20 実施例 17 で得られた 5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-(2-シアノフェノキシ)-1H-ベンズイミダゾール 25 mg のエタノール 2 ml 溶液に、50% ヒドロキシルアミン水溶液 0.1 ml を加え、反応液を 50 度にて 1 終夜攪拌した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=5/1) にて精製し、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.06 (3H, s), 5.12 (2H, s), 6.52 (1H, s), 6.80 (1H, d, $J=7.6\text{ Hz}$), 7.11 (2H, d, $J=8.6\text{ Hz}$), 7.28 (1H, t, $J=7.6\text{ Hz}$), 7.

25

4.7 (1H, dd, $J=7.8\text{ Hz}$, 4.3 Hz), 7.66 (1H, d, $J=7.6\text{ Hz}$), 7.66 (1H, s), 7.89 (2H, d, $J=8.6\text{ Hz}$), 7.96 (1H, t, $J=7.8\text{ Hz}$), 8.55 (1H, d, $J=7.8\text{ Hz}$), 8.65 (1H, d, $J=4.3\text{ Hz}$)

5 ESI-MS (m/e): 516 $[M+H]$

実施例 6 2

5-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-6-(2-(2-オキソ-4, 5-ジヒドロ-[1, 2, 4]-オキサジアゾール-3-イル)-フェノキシ)-1H-ベンズイミダゾール

実施例 6 1 で得られた 5-(2-(N-ヒドロキシカルバミドイル)-フェノキシ)-2-ピリジン-2-イル-6-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミダゾール 8 mg を N-メチルピロリジノン 0.25 ml 溶液に、1, 1'-カルボニルジイミダゾール 10 mg を加え、反応液を 70 度にて 4 時間攪拌した。反応混合物を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションを酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を無色固体として得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 3.12 (3H, s), 6.84 (2H, d, $J=8.6\text{ Hz}$), 6.82-6.88 (1H, m), 7.19 (1H, t, $J=7.2\text{ Hz}$), 7.41-7.47 (2H, m), 7.82 (2H, d, $J=8.6\text{ Hz}$), 7.91-7.97 (2H, m), 8.44 (1H, d, $J=7.8\text{ Hz}$), 8.69 (1H, d, $J=4.3\text{ Hz}$)

25 ESI-MS (m/e): 542 $[M+H]$

実施例 6 3

5-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-6-(2-[1, 2, 4]-オキサジアゾール-3-イル-フェノキシ)-1H-

ベンズイミダゾール

実施例 61 で得られた 5-(2-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-2-ピリジン-2-イル-6-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミダゾール 8mg の N-メチルピロリジノン 0.25 ml 溶液に、オルトギ酸エチル 0.5 ml を加え、反応液を 100 度にて 3 時間攪拌した。反応混合物を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションの溶媒を減圧留去した後、分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 574 4 (メルク 社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を黄色固体として得た。

¹H NMR (CDCl₃) δ: 3.03 (3H, s), 6.85-6.97 (3H, m), 7.23 (1H, t, J=7.8 Hz), 7.40-7.45 (3H, m), 7.68-7.74 (3H, m), 7.91 (1H, t, J=7.8 Hz), 8.03 (1H, d, J=7.8 Hz), 8.42 (1H, d, J=7.8 Hz), 8.65-8.68 (2H, m)
ESI-MS (m/e): 526 [M+H]

実施例 64

20 5-(ピリジン-3-イルオキシ)-2-ピリジン-2-イル-6-(2-(5-メチル-[1,2,4]-オキサジアゾール-3-イル)-フェノキシ)-1H-ベンズイミダゾール

実施例 5 で得られた 5-(2-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例 61 と同様の方法で得られた 5-(2-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール 20mg のピリジン 0.5 ml 溶液に、無水酢酸 0.3 ml を加え、反応液を 60 度にて終夜攪拌した。溶媒を減圧留去した後、分取用薄層クロマトグラフィー (KieselgelTM 60

F₂₅₄、Art 5744（メルク社製）、クロロホルム／メタノール＝10／1）にて精製し、表題化合物を淡黄色固体として得た。

¹HNMR (CDCl₃) δ: 6.80–7.00 (1H, m), 7.00–7.30 (4H, m), 7.30–7.44 (2H, m), 7.44–7.68 (1H, m), 7.86 (1H, td, J=7.6 Hz, 2.0 Hz), 7.97 (1H, dd, J=2.0 Hz, 7.6 Hz), 8.38 (1H, d, J=7.6 Hz), 8.60 (1H, d, J=4.8 Hz)
ESI-MS (m/e): 463 [M+H]

10 実施例 65

5-(4-メチル-ピリジン-3-スルホニル)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 13 で得られた 5-(2-メチル-ピリジン-5-イルスルファニル)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール 42 mg のテトラヒドロフラン 1.5 ml 溶液に、OXONE 92 mg、及び水 0.1 ml を加え、反応液を室温にて一終夜攪拌した。溶媒を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製した。得られたフラクションに飽和炭酸水素ナトリウム水を加えた後、クロロホルムにて抽出し、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、表題化合物を得た。

¹HNMR (CDCl₃) δ: 2.63 (3H, s), 7.23 (1H, s), 7.32 (1H, d, J=7.6 Hz), 7.44–7.50 (3H, m), 7.93 (1H, t, J=7.6 Hz), 8.09–8.14 (1H, m), 8.28 (1H, d, J=2.8 Hz), 8.36–8.41 (2H, m), 8.60, 8.61 (tautomer, 1H, s), 8.68 (1H, d, J=4.8 Hz), 8.93, 8.95 (tautomer, 1H, d, J=2.0 Hz)

ESI-MS (m/e): 444 [M+H]

実施例 6 6

5 - (4 - メタンスルホニル - フェノキシ) - 2 - (1 - オキシ - ピリジン - 2 - イル) - 6 - (2 - カルバモイル - フェノキシ) - 1H - ベンズイミダゾール

実施例 4 8 で得られた 5 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (2 - カルバモイル - フェノキシ) - 1H - ベンズイミダゾール 8.0 mg のクロロホルム 2 ml 溶液に、メタクロロ過安息香酸 15 mg を加え、反応液を室温にて 1 時間攪拌した。反応溶媒を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー [ODS - AS - 360 - CC (YMC 社製) 移動相：水 - アセトニトリル - 0.1% トリフルオロ酢酸] にて精製した。得られたフラクションの溶媒を減圧留去することにより、表題化合物を黄色固体として得た。

$^1\text{H-NMR}$ (CD_3OD) δ : 3.12 (3H, s), 6.87 (1H, d, $J = 7.8 \text{ Hz}$), 7.00 (2H, d, $J = 7.8 \text{ Hz}$), 7.18 (1H, t, $J = 7.8 \text{ Hz}$), 7.43 (1H, t, $J = 7.8 \text{ Hz}$), 7.69 - 7.76 (2H, m), 7.84 - 7.86 (3H, m), 7.92 (1H, d, $J = 7.8 \text{ Hz}$), 8.52 (1H, d, $J = 7.0 \text{ Hz}$), 8.64 (1H, d, $J = 7.8 \text{ Hz}$)

ESI-MS (m/e): 517 [$M+H$]

実施例 6 7

4 - (2 - メトキシ - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (ピリジン - 3 - イルオキシ) - 1H - ベンズイミダゾール

(工程 1)

5 - フルオロ - 3 - (2 - メトキシフェノキシ) - 2 - ニトロアニリンの合成

2 - メトキシフェノール 1.64 g のテトラヒドロフラン 30 ml 溶液に、氷冷下、水素化ナトリウム 528 mg を加え、反応液を同温度にて 30 分間攪

拌した。続いて、ジャーナル オブ オーガニック ケミストリー (Journal of Organic Chemistry)、1978年 第43巻、6号、1241頁-1243頁に記載されている方法にて合成した3, 5-ジフルオロ-2-ニトロアニリン1.91gを加え、反応液を室温にて2
5 日間攪拌した。反応液を水に注ぎ酢酸エチルで抽出後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル=5/1~4/1) にて精製し、表題化合物を橙色固体として得た。

(工程2)

- 10 3-(2-メトキシフェノキシ)-2-ニトロ-5-(ピリジン-3-イルオキシ)-アニリンの合成

5-フルオロ-3-(2-メトキシフェノキシ)-2-ニトロアニリン3.03gのジメチルホルムアミド30ml溶液に、3-ヒドロキシピリジン1.24g、及び炭酸カリウム5.42gを加え、反応液を90度にて終夜攪拌し
15 た。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル=2/1~1/1~1/2) にて精製し、表題化合物を橙色固体として得た。

(工程3)

- 20 3-(2-メトキシフェノキシ)-5-(ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミンの合成

3-(2-メトキシフェノキシ)-2-ニトロ-5-(ピリジン-3-イルオキシ)-アニリン1.33gのメタノール20ml溶液に、20%水酸化パラジウム-炭素触媒1gを加え、反応液を水素雰囲気下、4時間攪拌した。触
25 媒を濾去後、溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル=1/2~酢酸エチル) にて精製し、表題化合物を淡橙色油状物質として得た。

(工程4)

4-(2-メトキシフェノキシ)-2-ピリジン-2-イル-6-(ピリ

ジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

- 3-(2-メトキシフェノキシ)-5-(ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン59mgのニトロベンゼン0.5ml溶液に、ピリジン-2-カルボキサアルデヒド0.026mlを120度にて加え、反応液
- 5 を同温度にて1時間攪拌した。反応混合物を、シリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=1/1~酢酸エチル~クロロホルム/メタノール=20/1)にて精製した。得られたフラクションの溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー(KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=
- 10 20/1)にて精製し、表題化合物を淡黄色固体として得た。

¹HNMR (CDCl₃) δ: 3.79 and 3.83 (total 3H, each s), 6.20-7.40 (9H, m), 7.80-7.88 (1H, m), 8.24-8.65 (4H, m), 10.68-10.94 (1H, m)

- 15 ESI-MS (m/e): 411 [M+H]

実施例68

4-(4-フルオロフェノキシ)-2-ピラジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 20 4-フルオロフェノール、及び3-ヒドロキシピリジンを用いて、実施例67と同様の方法で合成した3-(4-フルオロフェノキシ)-5-(ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン46.7mgのピリジン2ml溶液に、ピラジン-2-カルボン酸18.6mg及び1-エチル-3-(3'-ジメチルアミノプロピル)-カルボジイミド塩酸塩57.5mgを加え、
- 25 反応液を終夜攪拌した後、ピリジンを減圧留去した。残渣を酢酸エチルにて希釈し、水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去することにより、アミド体の混合物を黄色油状物質として得た。得られたアミド体の混合物をトルエン3mlに溶解し、p-トルエンスルホン酸一水和物28mgを加え、反応液を120度にて終夜攪拌した。反応液を、酢酸エチルにて希

釈し、飽和重曹水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄、Art 5744 (メルク社製)、クロロホルム/メタノール=20/1) にて精製し、表題化合物を黄色固体として得た。

- 5 ¹H NMR (CDCl₃) δ: 6.35 and 6.53 (total 1H, each d, J=2.0 Hz), 6.77–7.31 (7H, m), 8.32–8.40 (2H, m), 8.54 and 8.56 (total 1H, each d, J=1.8 Hz), 8.61 and 8.64 (total 1H, each d, J=2.6 Hz), 9.59 and 9.69 (total 1H, each d, J=1.5 Hz), 10.60 (1H, br s)
- 10 ESI-MS (m/e): 400 [M+H]

実施例 69

- 15 6-(4-メトキシフェノキシ)-4-(1-メチル-1H-イミダゾール-2-イルスルファニル)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 1-メチル-1H-イミダゾール-2-チオール及び4-メトキシフェノールを順次用いて、実施例 67 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡褐色固体として得た。
- 20

- ¹H NMR (CDCl₃) δ: 3.73 and 3.74 (total 3H, each s), 3.81 (3H, s), 6.31–7.39 (9H, m), 7.78–7.88 (1H, m), 8.30 and 8.41 (total 1H, each d, J=7.8 Hz), 8.59 and 8.73 (total 1H, each d, J=4.5 Hz)
- 25 ESI-MS (m/e): 430 [M+H]

実施例 70

6-(4-メトキシフェノキシ)-2-ピリジン-2-イル-4-(ピリジ

ン-2-イルスルファニル)-1H-ベンズイミダゾール

ピリジン-2-チオール、及び4-メトキシフェノールを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- 5 $^1\text{H NMR}$ (CDCl_3) δ : 3.80 and 3.81 (total 3H, each s), 6.86-7.50 (10H, m), 7.75-7.88 (1H, m), 8.32-8.62 (3H, m)
ESI-MS (m/e): 427 [M+H]

10 実施例71

6-(3-メトキシフェノキシ)-4-(2-メトキシフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 実施例67(工程2)で得られた3-(2-メトキシフェノキシ)-2-ニトロ-5-(ピリジン-3-イルオキシ)-アニリン、及び3-メトキシフェノールを用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 15 $^1\text{H NMR}$ (CDCl_3) δ : 3.75 (3H, s), 3.79 and 3.84 (total 3H, each s), 6.24-7.23 (10H, m), 7.29-7.39 (1H, m), 7.79-7.89 (1H, m),
20 8.37 and 8.53 (total 1H, each d, $J=7.5$ Hz), 8.56-8.65 (1H, m), 10.53-10.83 (1H, m)
ESI-MS (m/e): 440 [M+H]

25 実施例72

4-(2-メトキシフェノキシ)-6-(ピリジン-3-イルオキシ)-2-チアゾール-2-イル-1H-ベンズイミダゾール

実施例67(工程3)で得られた3-(2-メトキシフェノキシ)-5-(ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及び2-チア

ゾールカルボキサアルデヒドを用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

^1H NMR (CDCl_3) δ : 3.78 and 3.82 (total 3H, each s), 6.20 and 6.44 (total 1H, each s), 6.68–7.28 (7H, m), 7.43–7.53 (1H, m), 7.88–7.98 (1H, m), 8.29–8.41 (2H, m), 10.90–11.10 (1H, m)
ESI-MS (m/e): 417 [M+H]

10

実施例73

4-(2-フルオロフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

2-フルオロフェノールを用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 6.18–6.78 (2H, m), 6.98–7.42 (8H, m), 7.72–7.90 (1H, m), 8.22–8.66 (3H, m), 11.3 (1H, brs)
ESI-MS (m/e): 399 [M+H]

20

実施例74

4-(4-フルオロフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

4-フルオロフェノールを用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 6.39 (1H, d, $J=2.1\text{ Hz}$), 6.84 (1H, d, $J=2.1\text{ Hz}$), 7.17–7.25 (4H, m), 7.39 (1H, dd, $J=8.4, 4.7\text{ Hz}$), 7.45 (1H, ddd, $J=8.4, 2.8, 1.5\text{ Hz}$), 7.50 (1H, dd, $J=7.7, 4.9\text{ Hz}$)

z)、7.96 (1H, ddd, $J=7.7, 7.7, 1.8$ Hz)、8.22 (1H, d, $J=7.7$ Hz)、8.33 (1H, dd, $J=4.7, 1.5$ Hz)、8.38 (1H, d, $J=2.8$ Hz)、8.69 (1H, ddd, $J=4.9, 1.8, 1.1$ Hz)

5 ESI-MS (m/e): 399 [M+H]

実施例 7 5

4-(3-フルオロフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

10 3-フルオロフェノールを用いて、実施例 6 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡褐色固体として得た。

^1H NMR (CDCl_3) δ : 6.47-6.98 (5H, m), 7.19-7.39 (4H, m), 7.78-7.89 (1H, m), 8.29-8.48

15 (3H, m), 8.58 (1H, s)

ESI-MS (m/e): 399 [M+H]

実施例 7 6

2-ピリジン-2-イル-4,6-ビス(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

20 3-ヒドロキシピリジンを用いて、実施例 6 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 7.07 (1H, d, $J=2.0$ Hz), 7.30 (1H, d, $J=2.0$ Hz), 7.54 (1H, ddd, $J=7.6$ Hz, 4.8 Hz, 1.2 Hz), 7.85-7.95 (2H, m), 7.98 (1H, td, $J=7.6$ Hz, 2.0 Hz), 8.10-8.40 (2H, m), 8.22 (1H, d, $J=8.8$ Hz), 8.48-8.60 (2H, m), 8.66 (1H, d, $J=2.2$ Hz), 8.70-8.82 (2H, m)

ESI-MS (m/e): 382 [M+H]

実施例 77

4-(2-シアノフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-2-イルオキシ)-1H-ベンズイミダゾール

- 5 2-シアノフェノール、及び2-ヒドロキシピリジンを順次用いて、実施例 67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 6.60-7.40 (3H, m), 6.92 (1H, d, $J=8.0\text{ Hz}$), 6.99 (1H, dd, $J=6.4\text{ Hz}$, 5.2 Hz), 7.15 (1H, t, $J=8.0\text{ Hz}$), 7.46 (1H, dd, $J=8.0\text{ Hz}$, 2.4 Hz), 7.58-7.70 (2H, m), 7.70-7.90 (1H, m), 8.18 (1H, dd, $J=4.8\text{ Hz}$, 1.2 Hz), 8.38 (1H, d, $J=8.0\text{ Hz}$), 8.60 (1H, d, $J=4.0\text{ Hz}$), 10.40-11.00 (1H, m)

15 ESI-MS (m/e): 406 $[\text{M}+\text{H}]$

実施例 78

4-(2-シアノフェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 20 2-シアノフェノールを用いて、実施例 67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 6.55 (1/2H, s), 6.69 (1/2H, s), 6.70-7.55 (8H, m), 7.58-7.72 (1H, m), 7.76-7.80 (1H, m), 8.26-8.48 (3H, m), 8.55-8.64 (1H, m), 10.8-11.4 (1H, m)

25 ESI-MS (m/e): 406 $[\text{M}+\text{H}]$

実施例 79

4-(2-メトキシカルボニルフェノキシ)-2-ピリジン-2-イル-
6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール・ニトリフル
オロ酢酸塩

2-ヒドロキシ安息香酸 メチルエステルを用いて、実施例67と同様の方
5 法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化
合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.70 (3H, s), 6.38 (1H, s),
7.14 (1H, s), 7.34 (1H, d, $J=7.6\text{ Hz}$), 7.39 (1
H, t, $J=7.6\text{ Hz}$), 7.50-7.75 (3H, m), 7.75-7.
10 88 (1H, m), 7.99 (1H, dd, $J=7.6\text{ Hz}$, 1.2 Hz),
8.07 (1H, t, $J=7.6\text{ Hz}$), 8.27-8.58 (3H, m),
8.72-8.88 (1H, m)
ESI-MS (m/e): 439 [M+H]

15 実施例80

4-(2-アセチルフェノキシ)-2-(ピリジン-2-イル)-6-(ピ
リジン-3-イルオキシ)-1H-ベンズイミダゾール

2-ヒドロキシアセトフェノンを用いて、実施例67と同様の方法、これに
準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 2.68 (3H, s), 6.58 (1H, d, J
= 2.3 Hz), 7.19 (1H, dd, $J=1.2$, 8.2 Hz), 7.3
1 (1H, dd, $J=1.2$, 7.5 Hz), 7.35 (1H, dd, $J=1.$
0, 7.5 Hz), 7.53-7.62 (2H, m), 7.69 (1H, dd,
 $J=4.7$, 7.8 Hz), 7.76-7.82 (1H, m), 7.87 (1
25 H, dd, $J=1.0$, 8.2 Hz), 8.10 (1H, t, $J=7.8\text{ H}$
z), 8.50-8.52 (1H, m), 8.54 (1H, d, $J=2.3\text{ H}$
z), 8.62 (1H, d, $J=7.0\text{ Hz}$), 8.74 (1H, d, $J=4.$
7 Hz)
ESI-MS (m/e): 423 [M+H]

実施例 8 1

4-(1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

3-ヒドロキシ-1-メチル-1H-ピリジン-2-オンを用いて、実施例 6 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 3. 62 (3H, s), 6. 02-7. 40 (8 H, m), 7. 84 (1H, t, $J=7. 2\text{ Hz}$), 8. 33 (1H, d, $J=4. 4\text{ Hz}$), 8. 33-8. 50 (2H, m), 8. 52-8. 70 (1 H, m)

ESI-MS (m/e): 412 [$M+H$]

15 実施例 8 2

6-(4-ジメチルカルバモイル-フェノキシ)-4-(1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

3-ヒドロキシ-1-メチル-1H-ピリジン-2-オン、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例 6 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

^1H NMR (CDCl_3) δ : 3. 03 and 3. 09 (total 6H, each s), 3. 60 and 3. 64 (total 3H, each s), 6. 08-6. 15 (1H, m), 6. 42 and 6. 64 (total 1H, each s), 6. 82-7. 41 (8H, m), 7. 80-7. 88 (1H, m), 8. 36 and 8. 45 (total 1H, each d, $J=8. 2\text{ Hz}$), 8. 59 and 8. 64 (total 1H, each d, $J=4. 5\text{ Hz}$)

ESI-MS (m/e) : 482 [M+H]

実施例 8 3

4- (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) -6- (4-ジ
5 メチルカルバモイル-フェノキシ) -2-ピリジン-2-イル-1H-ベンズ
イミダゾール

2-ジフルオロメトキシ-3-ヒドロキシピリジン、及び4-ヒドロキシ-
N, N-ジメチルベンズアミドを順次用いて、実施例 6 7 と同様の方法、これ
に準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡
10 黄色固体として得た。

^1H NMR (CDCl_3) δ : 3.02 and 3.09 (total 6H,
each s), 6.36 and 6.48 (total 1H, each
s), 6.84-7.67 (9H, m), 7.83 and 7.88 (to
tal 1H, each t, $J=7.8\text{Hz}$), 7.99 and 8.0
15 0 (total 1H, each d, $J=5.0\text{Hz}$), 8.40 and
8.42 (total 1H, each d, $J=8.4\text{Hz}$), 8.61
and 8.64 (total 1H, each d, $J=4.3\text{Hz}$)

ESI-MS (m/e) : 518 [M+H]

20 実施例 8 4

6- (2-メチル-ピリジン-5-イルスルファニル) -2- (ピリジン-
2-イル) -4- (ピリジン-3-イルオキシ) -1H-ベンズイミダゾール

3-ヒドロキシピリジン、及び6-メチルピリジン-3-チオールを順次用
いて、実施例 6 7 と同様の方法、これに準じた方法又はこれらと常法とを組み
25 合わせるにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 2.52 (3H, s), 6.66-6.80 (1
H, brs), 7.05 (1H, d, $J=8.0\text{Hz}$), 7.20-7.28
(3H, m), 7.32 (1H, m), 7.49 (1H, dd, $J=2.0\text{H}$
z, 8.0Hz), 7.81 (1H, t, $J=7.6\text{Hz}$), 8.32-8.

4.0 (3H, m), 8.44 (1H, d, $J=2.0$ Hz), 8.52 (1H, d, $J=4.8$ Hz), 11.70–12.0 (1H, br s)

ESI-MS (m/e): 412 [M+H]

5 実施例 85

4-(2-シアノフェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイルフェノキシ)-1H-ベンズイミダゾール

2-シアノフェノール、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常

10 法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CDCl_3) δ : 3.05 (3H, s), 3.18 (3H, s), 6.62 (1H, s), 6.92–7.08 (3H, m), 7.00 (2H, d, $J=8.8$ Hz), 7.10–7.20 (2H, m), 7.36–7.50 (4H, m), 7.40 (2H, d, $J=8.8$ Hz), 7.63 (1H, d, $J=6.3$ Hz), 7.89 (1H, t, $J=7.8$ Hz), 8.44 (1H, d, $J=7.8$ Hz), 8.61 (1H, d, $J=3.9$ Hz)

ESI-MS (m/e): 476 [M+H]

実施例 86

20 4-(2-フルオロフェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイルフェノキシ)-1H-ベンズイミダゾール

2-フルオロフェノール、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

25 ^1H NMR (CDCl_3) δ : 3.02 (3H, s), 3.10 (3H, s), 6.39 (1H, s), 6.92–7.00 (3H, m), 6.96 (2H, d, $J=9.0$ Hz), 7.10–7.24 (4H, m), 7.36–7.42 (3H, m), 7.39 (2H, d, $J=9.0$ Hz), 7.88 (1H, d, $J=7.7$ Hz), 8.51 (1H, d, $J=8.0$ Hz), 8.63

(1H, d, J=7.7 Hz)

ESI-MS (m/e) : 469 [M+H]

実施例 87

5 4-(2-フルオロフェノキシ)-2-(ピリジン-2-イル)-6-(4-メタンスルホニルフェノキシ)-1H-ベンズイミダゾール

2-フルオロフェノール、及び4-(メタンスルホニル)フェノールを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

10 ¹HNMR (CDCl₃) δ : 3.08 (3H, s), 6.44 (1H, s),
7.08 (2H, d, J=9.0 Hz), 7.18-7.57 (5H, m),
7.59 (1H, dd, J=3.1, 8.2 Hz), 7.90 (2H, d, J
=9.0 Hz), 8.06 (1H, t, J=7.6 Hz), 8.64 (1H,
d, J=8.2 Hz), 8.71 (1H, d, J=7.6 Hz)

15 ESI-MS (m/e) : 476 [M+H]

実施例 88

20 4-(2-(1-ヒドロキシエチル)フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイルフェノキシ)-1H-ベンズイミダゾール

2-(1-ヒドロキシエチル)フェノール、及び4-ヒドロキシ-N,N-ジメチルベンズアミドを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

25 ¹HNMR (CDCl₃) δ : 1.48 (3H, d, J=6.4 Hz), 3.0
5 (3H, s), 3.10 (3H, s), 5.26 (1H, q, J=6.4 Hz),
6.34 (1H, s), 7.04 (2H, d, J=9.0 Hz), 7.
05-7.10 (2H, m), 7.29-7.33 (2H, m), 7.44
(2H, d, J=9.0 Hz), 7.57 (1H, dd, J=4.7, 7.6
Hz), 7.68 (1H, dd, J=2.0, 7.4 Hz), 8.04 (1H,

d t, $J=1.6, 7.8\text{ Hz}$), 8.37 (1H, d, $J=7.8\text{ Hz}$),
8.80 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 495 [M+H]

5 実施例 89

4-(2-メタンスルホニルフェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイルフェノキシ)-1H-ベンズイミダゾール

2-(メタンスルホニル)フェノール、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例 67 と同様の方法、これに準じた方

10 法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.06 (3H, s), 3.14 (3H, s),
3.49 (3H, s), 7.03 (1H, d, $J=2.0\text{ Hz}$), 7.11
(2H, d, $J=8.8\text{ Hz}$), 7.22 (1H, d, $J=8.0\text{ Hz}$), 7.
32-7.40 (2H, m), 7.42 (1H, d, $J=2.0\text{ Hz}$), 7.
15 48 (2H, d, $J=9.0\text{ Hz}$), 7.57 (1H, dd, $J=4.9, 7.$
8 Hz), 7.63 (1H, dd, $J=1.8, 7.9\text{ Hz}$), 8.00 (1
H, d t, $J=1.6, 7.8\text{ Hz}$), 8.14 (1H, dd, $J=1.8,$
8.0 Hz), 8.52 (1H, d, $J=8.0\text{ Hz}$), 8.75 (1H, d,
 $J=4.9\text{ Hz}$)

20 ESI-MS (m/e): 529 [M+H]

実施例 90

4-(2-アセチルフェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイルフェノキシ)-1H-ベンズイミダゾール

25 2-ヒドロキシアセトフェノン、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例 67 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.68 (3H, s), 3.10 (3H, s),
3.20 (3H, s), 6.67 (1H, s), 7.05 (2H, d, $J=8.$

2 Hz), 7.15–7.22 (2H, m), 7.35 (1H, t, J=7.0 Hz), 7.45 (2H, d, J=8.2 Hz), 7.55 (1H, t, J=7.0 Hz), 7.60–7.64 (1H, m), 7.86 (1H, d, J=7.4 Hz), 8.08–8.14 (1H, m), 8.64 (1H, d, J=7.4 Hz), 8.75–8.77 (1H, m)

ESI-MS (m/e) : 493 [M+H]

実施例 9 1

4-(2-ジメチルカルバモイル-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾール

2-ヒドロキシ-N, N-ジメチルベンズアミド、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例 6 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CDCl₃) δ : 2.99 (3H, s), 3.06 (6H, s), 3.17 (3H, s), 6.91–6.94 (1H, m), 7.04 (2H, d, J=8.6 Hz), 7.06–7.10 (1H, m), 7.17 (1H, t, J=7.4 Hz), 7.28–7.39 (4H, m), 7.42 (2H, d, J=8.6 Hz), 7.84 (1H, t, J=7.8 Hz), 8.41 (1H, d, J=7.8 Hz), 8.68 (1H, d, J=3.9 Hz)

ESI-MS (m/e) : 522 [M+H]

実施例 9 2

4-(2, 5-ジフルオロ-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾール

2, 5-ジフルオロフェノール、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例 6 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CDCl₃) δ : 3.02 (3H, s), 3.14 (3H, s),

6. 52-6. 55 (1H, m), 6. 90-6. 99 (2H, m), 7. 02 (2H, d, J=8. 2Hz), 7. 10 (1H, d, J=2. 0Hz), 7. 16-7. 24 (1H, m), 7. 42 (2H, d, J=8. 2Hz), 7. 54-7. 60 (1H, m), 8. 06 (1H, dt, J=1. 6, 7. 8Hz), 8. 61 (1H, d, J=7. 8Hz), 8. 72 (1H, d, J=4. 7Hz)

ESI-MS (m/e) : 487 [M+H]

実施例 9 3

10 4-(2, 4-ジフルオロフェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイルフェノキシ)-1H-ベンズイミダゾール

2, 4-ジフルオロフェノール、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例 6 7と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

15 $^1\text{H NMR}$ (CDCl₃) δ : 3. 00 (3H, s), 3. 09 (3H, s), 6. 31 (1H, s), 6. 99 (1H, s), 7. 02 (2H, d, J=8. 6Hz), 7. 10-7. 25 (2H, m), 7. 28-7. 40 (1H, m), 7. 43 (2H, d, J=8. 6Hz), 7. 49-7. 52 (1H, m), 7. 98 (1H, d, J=7. 8Hz), 8. 34 (1H, d, J=7. 9Hz), 8. 74 (1H, d, J=3. 9Hz)

ESI-MS (m/e) : 487 [M+H]

実施例 9 4

25 4-(2, 6-ジフルオロフェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイルフェノキシ)-1H-ベンズイミダゾール

2, 6-ジフルオロフェノール、及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例 6 7と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl₃) δ : 3. 02 (3H, s), 3. 14 (3H, s),

6. 39 (1H, s), 7. 00 (2H, d, J=8. 6 Hz), 7. 06 –
 7. 18 (3H, m), 7. 20–7. 25 (1H, m), 7. 41 (2H,
 d, J=8. 6 Hz), 7. 48–7. 51 (1H, m), 7. 99 (1H,
 dt, J=1. 6, 7. 8 Hz), 8. 59 (1H, d, J=8. 2 Hz),
 5 8. 70 (1H, d, J=4. 3 Hz)

ESI-MS (m/e) : 487 [M+H]

実施例 95

4 – (2 – メトキシ – フェノキシ) – 2 – (ピリジン – 2 – イル) – 6 –
 10 (4 – メタンスルホニル – フェノキシ) – 1H – ベンズイミダゾール

4 – (メタンスルホニル) フェノールを用いて、実施例 71 と同様の方法、
 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
 を得た。

¹H NMR (CDCl₃) δ : 3. 03 (3H, s), 3. 79 (3H, s),
 15 6. 32 (1H, s), 6. 92–6. 99 (1H, m), 7. 00 (1H,
 s), 7. 06 (2H, d, J=8. 6 Hz), 7. 10–7. 22 (3H,
 m), 7. 38–7. 43 (1H, m), 7. 83 (2H, d, J=8. 6 Hz),
 7. 90 (1H, t, J=7. 8 Hz), 8. 50 (1H, d, J=7. 8 Hz),
 8. 64 (1H, d, J=4. 7 Hz)

20 ESI-MS (m/e) : 488 [M+H]

実施例 96

6 – (4 – ジメチルカルバモイル – フェノキシ) – 4 – (1 – エチル – 2 – オ
 キソ – 1, 2 – ジヒドロ – ピリジン – 3 – イルオキシ) – 2 – ピリジン – 2 –
 25 イル – 1H – ベンズイミダゾール

1 – エチル – 3 – ヒドロキシ – 1H – ピリジン – 2 – オン、及び 4 – ヒドロ
 キシー – N, N – ジメチルベンズアミドを順次用いて、実施例 67 と同様の方法、
 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
 を淡黄色固体として得た。

¹HNMR (CDCl₃) δ : 1.38 (3H, t, J=6.8 Hz), 3.02 and 3.09 (total 6H, each s), 4.06 (2H, q, J=6.8 Hz), 6.15 (1H, t, J=7.0 Hz), 6.40–7.42 (9H, m), 7.78–7.86 (1H, m), 8.32–8.42 (1H, m), 8.57–8.66 (1H, m)
ESI-MS (m/e) : 496 [M+H]

実施例 97

6 – (6 – メチル – ピリジン – 3 – イルファニル) – 4 – (4 – メチル – 4
10 H – [1, 2, 4] トリアゾール – 3 – イルスルファニル) – 2 – (ピリジン – 2 – イル) – 1H – ベンズイミダゾール

4 – メチル – 4H – [1, 2, 4] トリアゾール – 3 – チオール、及び 6 –
メチル – ピリジン – 3 – チオールを順次用いて、実施例 67 と同様の方法、こ
れに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を
15 得た。

¹HNMR (CDCl₃) δ : 2.55 (3H, s), 3.71 (3H, s),
7.17 (1H, d, J=8.0 Hz), 7.20–7.24 (1H, br s), 7.42–7.46 (1H, m), 7.59 (1H, dd, J=2.4 Hz, 8.0 Hz), 7.66–7.68 (1H, br s), 7.91 (1H,
20 t, J=8.0 Hz), 8.32–8.38 (3H, m), 8.70 (1H, d, J=4.8 Hz)
ESI-MS (m/e) : 432 [M+H]

実施例 98

4 – (4 – フルオロフェノキシ) – 2 – (5 – メチル – イソオキサゾール –
25 3 – イル) – 6 – (ピリジン – 3 – イルオキシ) – 1H – ベンズイミダゾール

5 – メチル – イソオキサゾール – 3 – カルボン酸を用いて、実施例 68 と同様の
方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表
題化合物を白色固体として得た。

^1H NMR (DMSO- d_6) δ : 2.50 (3H, s), 6.40 (1H, s), 6.80 (1H, s), 6.82 (1H, brs), 7.14–7.24 (4H, m), 7.38 (1H, dd, $J=8.2, 4.7\text{ Hz}$), 7.44 (1H, d, $J=7.7\text{ Hz}$), 8.32 (1H, d, $J=4.7\text{ Hz}$),
 5 8.36 (1H, d, $J=2.5\text{ Hz}$)

ESI-MS (m/e): 403 [M+H]

実施例 99

4-(4-フルオロフェノキシ)-2-(1-メチル-1H-イミダゾール-4-イル)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

1-メチル-1H-イミダゾール-4-カルボン酸を用いて、実施例 68 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

15 ^1H NMR (DMSO- d_6) δ : 3.72 (3H, s), 6.38 (1H, d, $J=1.8\text{ Hz}$), 6.81 (1H, d, $J=1.8\text{ Hz}$), 7.05–7.13 (2H, m), 7.17 (2H, t, $J=8.8\text{ Hz}$), 7.36–7.43 (2H, m), 7.75 (1H, s), 7.78 (1H, d, $J=1.1\text{ Hz}$), 8.28 (1H, s), 8.35 (1H, d, $J=2.2\text{ Hz}$)

20 ESI-MS (m/e): 402 [M+H]

実施例 100

4-(4-フルオロフェノキシ)-2-(3-メチル-[1, 2, 4]チアジアゾール-5-イル)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール・トリフルオロ酢酸塩

特許EP 0726260に準じた方法及びこれらと常法とを組み合わせで合成した3-メチル[1, 2, 4]チアジアゾール-5-カルボン酸を用いて、実施例 68 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

^1H NMR (DMSO- d_6) δ : 2.70 (3H, s), 6.44 (1H, d, $J=2.2\text{ Hz}$), 6.87 (1H, s), 7.15–7.27 (4H, m), 8.39 (1H, dd, $J=4.5, 1.5\text{ Hz}$), 8.44 (1H, d, $J=2.5\text{ Hz}$)

5 ESI-MS (m/e): 420 [M+H]

実施例101

4-(4-フルオロフェノキシ)-2-イソオキサゾール-3-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 10 イソオキサゾール-3-カルボン酸を用いて、実施例68と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 6.41 (1H, d, $J=2.4\text{ Hz}$), 7.01 (1H, d, $J=2.4\text{ Hz}$), 7.02–7.20 (5H, m), 7.51 (1H, dd, $J=4.4\text{ Hz}, 8.4\text{ Hz}$), 7.59 (1H, dd, $J=2.4\text{ Hz}, 8.4\text{ Hz}$), 8.32 (1H, d, $J=4.4\text{ Hz}$), 8.35 (1H, d, $J=2.4\text{ Hz}$), 8.84 (1H, d, $J=2.4\text{ Hz}$)
15 ESI-MS (m/e): 389 [M+H]

20 実施例102

4-(4-フルオロフェノキシ)-2-ピリミジン-4-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

ピリミジン-4-カルボン酸を用いて、実施例68と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- 25 ^1H NMR (CDCl_3) δ : 2.60 (3H, s), 6.98–7.40 (8H, m), 8.30–8.50 (2H, m), 8.63 (1H, s), 10.40–11.00 (1H, m)
ESI-MS (m/e): 400 [M+H]

実施例 103

4-(4-フルオロフェノキシ)-2-ピリミジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 5 ピリミジン-2-カルボン酸を用いて、実施例 68 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H-NMR}$ (CD_3OD) δ : 6.42 (1H, s), 6.98 (1H, s), 7.10-7.30 (5H, m), 7.36-7.60 (2H, m), 8.22-8.42 (2H, m), 8.90-9.10 (1H, m), 9.20 (1H, s)

- 10 ESI-MS (m/e): 400 [M+H]

実施例 104

4-(4-フルオロフェノキシ)-2-(1H-イミダゾール-2-イル)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 15 1H-イミダゾール-2-カルボン酸を用いて、実施例 68 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- $^1\text{H-NMR}$ (CD_3OD) δ : 6.44 (1H, d, $J=2.0\text{ Hz}$), 7.00 (1H, d, $J=2.0\text{ Hz}$), 7.05-7.18 (4H, m), 7.25 (2H, s), 7.39 (1H, dd, $J=3.2\text{ Hz}$, 8.4 Hz), 7.42-7.50 (1H, m), 8.26 (1H, dd, $J=1.6\text{ Hz}$, 4.4 Hz), 8.29 (1H, d, $J=3.2\text{ Hz}$)

ESI-MS (m/e): 388 [M+H]

25 実施例 105

4-(4-フルオロフェノキシ)-2-(1-メチル-1H-イミダゾール-2-イル)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

1-メチル-1H-イミダゾール-2-カルボン酸を用いて、実施例 68 と

同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.98–4.38 (3H, m), 6.38–6.60 (1H, m), 6.60–6.80 (1H, m), 6.80–7.40

5 (8H, m), 8.20–8.44 (2H, m)

ESI-MS (m/e): 402 [M+H]

実施例106

10 4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-2-[1, 2, 4]チアジアゾール-5-イル-1H-ベンズイミダゾール

参考例1の方法で合成した[1, 2, 4]チアジアゾール-5-カルボン酸を用いて、実施例68と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色油状物質として得た。

15 $^1\text{H NMR}$ (CD_3OD) δ : 6.42 (1H, s), 6.90–7.23 (5H, m), 7.39–7.50 (2H, m), 8.25–8.32 (2H, m), 8.86 (1H, s)

ESI-MS (m/e): 406 [M+H]

実施例107

20 4-(2, 6-ジフルオロフェノキシ)-2-(ピラジン-2-イル)-6-(4-メタンスルホニルフェノキシ)-1H-ベンズイミダゾール

2, 6-ジフルオロフェノール、及び4-(メタンスルホニル)フェノールを順次用いて、実施例68と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 3.03 (3H, s), 6.28 (1H, s), 7.08 (1H, s), 7.17 (2H, d, $J=9.4\text{ Hz}$), 7.19–7.24 (2H, m), 7.30–7.40 (1H, m), 7.93 (2H, d, $J=9.4\text{ Hz}$), 8.70–8.75 (1H, m), 8.77–8.82 (1H, m), 9.55–9.60 (1H, m)

ESI-MS (m/e) : 495 [M+H]

実施例108-1、108-2

5 4-(2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール、及び4-(2-メトキシ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

10 3-ヒドロキシ-2-メトキシピリジン、3-ヒドロキシピリジン、及びピコリン酸を順次用いて、実施例68と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をそれぞれ得た。

4-(2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

15 $^1\text{H-NMR}$ (CDCl_3) δ : 6.10-7.35 (8H, m), 7.77-7.84 (1H, m), 8.30-8.41 (3H, m), 8.53 (1H, d, $J=4.4\text{ Hz}$)

ESI-MS (m/e) : 398 [M+H]

20 4-(2-メトキシ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

$^1\text{H-NMR}$ (CDCl_3) δ : 3.95 and 3.99 (total 3H, each s), 6.25 and 6.45 (total 1H, each s), 6.80-7.45 (6H, m), 7.79-7.90 (1H, m),
25 8.00 (1H, d, $J=1.5\text{ Hz}$), 8.30-8.63 (4H, m)

ESI-MS (m/e) : 412 [M+H]

実施例109-1、109-2

6-(4-ジメチルカルバモイル-フェノキシ)-4-(2-メトキシ-ピリ

ジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール、及び6-(4-ジメチルカルバモイル-フェノキシ)-4-(2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 5 3-ヒドロキシ-2-メトキシピリジン、4-ヒドロキシ-N, N-ジメチルベンズアミド、及びピコリン酸を順次用いて、実施例108-1、108-2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をそれぞれ得た。

10 6-(4-ジメチルカルバモイル-フェノキシ)-4-(2-メトキシ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- ¹HNMR (CDCl₃) δ: 3.03 and 3.08 (total 6H, each s), 3.95 and 4.00 (total 3H, each s), 6.27 and 6.47 (total 1H, each d, J=1.8Hz), 6.80-7.45 (8H, m), 7.80-7.91 (1H, m), 7.98-8.03 (1H, m), 8.38 and 8.48 (total 1H, each d, J=7.8Hz), 8.61 and 8.64 (total 1H, each d, J=4.8Hz)

ESI-MS (m/e): 482 [M+H]

20

6-(4-ジメチルカルバモイル-フェノキシ)-4-(2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 25 ¹HNMR (CDCl₃) δ: 3.03 and 3.08 (total 6H, each s), 6.18 and 6.23 (total 1H, each t, J=7.0Hz), 6.52 and 6.73 (total 1H, each d, J=1.8Hz), 6.80-7.42 (8H, m), 7.79 and 7.84 (total 1H, each t, J=7.8Hz), 8.37 and 8.40 (total 1H, each d, J=7.8H

z), 8.56 and 8.57 (total 1H, each d, J=5.0 Hz)

ESI-MS (m/e) : 468 [M+H]

5 実施例 110

4-(2-カルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール・ニトリフルオロ酢酸塩

10 実施例 78 で得られた 4-(2-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CD₃OD) δ : 6.61 (1H, d, J=2.0 Hz), 7.19 (1H, d, J=8.0 Hz), 7.22 (1H, s), 7.31 (1H, td, J=7.6 Hz, 1.2 Hz), 7.48-7.60 (2H, m), 7.72-7.80 (1H, m), 7.83 (1H, dd, J=7.6 Hz, 1.2 Hz), 7.87-7.95 (1H, m), 8.03 (1H, td, J=8.0 Hz, 1.2 Hz), 8.01 (1H, dd, J=7.6 Hz, 1.2 Hz), 8.45 (1H, d, J=5.2 Hz), 8.48-8.54 (1H, m), 8.76-8.84 (1H, m)

ESI-MS (m/e) : 424 [M+H]

実施例 111

4-(2-カルバモイル-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾール

25 実施例 85 で得られた 4-(2-シアノ-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾールを用いて、実施例 110 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 2.99 (3H, s), 3.08 (3H, s),
 6.56 (1H, s), 6.86–6.92 (1H, m), 6.95 (2H,
 $J=8.9\text{ Hz}$), 7.04–7.08 (2H, m), 7.30–7.38
 (4H, m), 7.36 (2H, d, $J=8.9\text{ Hz}$), 7.52 (1H, d,
 $J=7.6\text{ Hz}$), 7.80 (1H, t, $J=7.9\text{ Hz}$), 8.36 (1H,
 d, $J=7.9\text{ Hz}$), 8.52 (1H, d, $J=3.7\text{ Hz}$)
 ESI-MS (m/e): 494 [M+H]

実施例112

10 4-(2-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾール

実施例85で得られた4-(2-シアノ-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾールを用いて、実施例61と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 3.02 (3H, s), 3.16 (3H, s),
 6.61 (1H, d, $J=2.0\text{ Hz}$), 6.95 (1H, d, $J=2.0\text{ Hz}$),
 6.97 (2H, d, $J=8.6\text{ Hz}$), 7.14–7.22 (2H,
 20 m), 7.38 (2H, d, $J=8.6\text{ Hz}$), 7.52 (1H, dd, $J=4.9, 7.6\text{ Hz}$),
 7.56–7.62 (1H, m), 7.63–7.67 (1H, m),
 7.97 (1H, dt, $J=1.6, 7.8\text{ Hz}$), 8.48 (1H, d, $J=7.8\text{ Hz}$),
 8.68 (1H, d, $J=4.9\text{ Hz}$)
 ESI-MS (m/e): 509 [M+H]

25

実施例113

4-(2-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾール

実施例 112 で得られた 4-(2-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾールを用いて、実施例 64 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、

5 表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 2.70 (3H, s), 3.02 (3H, s), 3.15 (3H, s), 6.91 (1H, s), 7.04 (2H, d, $J=8.6\text{ Hz}$), 7.30-7.38 (3H, m), 7.44 (2H, d, $J=8.6\text{ Hz}$), 7.50-7.58 (2H, m), 7.95 (1H, d, $J=7.8\text{ Hz}$), 8.02 (1H, t, $J=7.8\text{ Hz}$), 8.63 (1H, d, $J=8.6\text{ Hz}$), 8.71 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 533 [$M+H$]

実施例 114

15 4-(2-(5-オキソ-4, 5-ジヒドロ-[1, 2, 4]オキサジアゾール-3-イル)-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾール

実施例 112 で得られた 4-(2-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-2-(ピリジン-2-イル)-6-(4-ジメチルカルバモイル-フェノキシ)-1H-ベンズイミダゾールを用いて、実施例 62 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 3.04 (3H, s), 3.15 (3H, s), 6.74 (1H, s), 6.99 (2H, d, $J=8.6\text{ Hz}$), 7.10 (1H, s), 7.28-7.36 (2H, m), 7.44 (2H, d, $J=8.6\text{ Hz}$), 7.50-7.58 (2H, m), 7.89 (1H, d, $J=7.8\text{ Hz}$), 8.00-8.07 (1H, m), 8.56-8.64 (2H, m)

ESI-MS (m/e): 535 [$M+H$]

実施例 115

4-(4-フルオロフェノキシ)-2-(ピラゾール-1-イル)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

5 (工程 1)

4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール-2-チオール

実施例 68 で得られた 3-(4-フルオロフェノキシ)-5-(ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン 273 mg のエタノール 2.0 ml 溶液に、二硫化炭素 0.06 ml、および水酸化カリウム 54 mg を加え、反応液を 80 度にて一終夜撹拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、表題化合物を得た。

(工程 2)

15 4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール-2-イル)-ヒドラジンの合成

4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール-2-チオール 130 mg に、ヒドラジン-水和物 1.0 ml を加え、反応液を 130 度にて一終夜撹拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、ヘキサン/酢酸エチル=1/1) にて精製し、表題化合物を得た。

(工程 3)

25 4-(4-フルオロフェノキシ)-2-(ピラゾール-1-イル)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

(4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール-2-イル)-ヒドラジン 8.3 mg のエタノール 0.3 ml 溶液に、テトラメトキシプロパン 0.012 ml を加え、反応液

を80度にて一終夜攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=9/1) にて精製し、表題化合物を得た。

- 5 ¹H NMR (CDCl₃) δ: 6.36 (1H, d, J=2.6 Hz), 6.48–6.51 (2H, m), 6.77 (1H, d, J=2.6 Hz), 7.05 (2H, d, J=6.9 Hz), 7.11–7.18 (1H, m), 7.22–7.28 (2H, m), 7.72–7.75 (1H, m), 8.30–8.38 (2H, m), 8.48 (1H, d, J=3.8 Hz)
- 10 ESI-MS (m/e): 388 [M+H]

実施例 116

4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-2-[1, 2, 4] トリアゾール-1-イル-1H-ベンズイミダゾール

15 (工程 1)

4-(4-フルオロフェノキシ)-2-メチルスルファニル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの合成

- 実施例 115 により合成した 4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール-2-チオール 78 mg
20 g のジメチルホルムアミド 1.0 ml 溶液に、炭酸カリウム 30 mg およびヨウ化メチル 0.014 ml を加え、反応液を 0 度にて 30 分間攪拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、表題化合物を得た。

(工程 2)

- 25 4-(4-フルオロフェノキシ)-2-メタンスルホンイル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの合成

4-(4-フルオロフェノキシ)-2-メチルスルファニル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール 80 mg のクロロホルム 1.0 ml 溶液に、メタクロロ過安息香酸 84 mg を加え、反応液を 0 度にて

30分間撹拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、酢酸エチル) にて精製し、表題化合物を得た。

5 (工程3)

4-(4-フルオロフェノキシ)-6-(ピリジン-3-イルオキシ)-2-[1, 2, 4]トリアゾール-1-イル-1H-ベンズイミダゾールの製造

10 4-(4-フルオロフェノキシ)-2-メタンスルホニル-6-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール 16 mg のジメチルホルムアミド 0.5 ml 溶液に、水素化ナトリウム 5.0 mg を加えた後、[1, 2, 4]-トリアゾール 10.4 mg を加え、反応液を 160 度にて一終夜撹拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層
15 クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、酢酸エチル) にて精製し、表題化合物を得た。

¹H NMR (CDCl₃) δ: 6.42 (1H, s), 7.03-7.15 (3H, m), 7.19 (1H, s), 7.27-7.32 (3H, m), 8.12 (1H, s), 8.32-8.38 (2H, m), 9.15 (1H, s)

20 ESI-MS (m/e): 389 [M+H]

実施例 117

5-クロロ-2-ピリジン-2-イル-4, 6-ビス-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

25 (工程1)

3-クロロ-2, 4-ビス(ピリジン-3-イルオキシ)-ニトロベンゼンの合成

[1, 2, 3]-トリクロロ-4-ニトロベンゼン 679 mg のジメチルホルムアミド 8 ml 溶液に、3-ヒドロキシピリジン 628 mg、及び炭酸カリ

ウム1. 82 gを加え、反応液を100度にて2時間攪拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィ（展開溶媒：ヘキサン／酢酸エチル＝1／1～酢酸エチル）にて精製し、表題化合物を淡黄色油状物質として得た。

5 (工程2)

3-クロロ-2, 4-ビス(ピリジン-3-イルオキシ) アニリンの合成

3-クロロ-2, 4-ビス(ピリジン-3-イルオキシ) ニトロベンゼン1. 2 gのメタノール15 mlと水7. 5 ml懸濁液に、塩化アンモニウム963 mg、及び鉄粉503 mgを加え、反応液を3時間加熱還流した。反応液を濾去後、溶媒を減圧留去した。残渣を酢酸エチルにて希釈し、水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィ（展開溶媒：ヘキサン／酢酸エチル＝1／1～酢酸エチル）にて精製し、表題化合物を淡黄色油状物質として得た。

15 (工程3)

3-クロロ-2, 4-ビス(ピリジン-3-イルオキシ) -6-ニトロアニリンの合成

3-クロロ-2, 4-ビス(ピリジン-3-イルオキシ) -アニリン891 mgのトリフルオロ酢酸20 ml溶液に、硝酸カリウム315 mgを加え、反応液を室温にて終夜攪拌した後、溶媒を減圧留去した。残渣を酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィ（展開溶媒：ヘキサン／酢酸エチル＝1／1～酢酸エチル）にて精製し、表題化合物を橙色固体として得た。

25 (工程4)

4-クロロ-3, 5-ビス(ピリジン-3-イルオキシ) -ベンゼン-1, 2-ジアミンの合成

3-クロロ-2, 4-ビス(ピリジン-3-イルオキシ) -6-ニトロアニリン143 mgのメタノール8 mlと水4 ml懸濁液に、塩化アンモニウム1

28 mg、及び鉄粉67 mgを加え、反応液を2時間加熱還流した。反応液を濾去後、溶媒を減圧留去した。残渣を酢酸エチルにて希釈し、水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、表題化合物を淡褐色固体として得た。

5 (工程5)

5-クロロ-2-ピリジン-2-イル-4, 6-ビス-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

4-クロロ-3, 5-ビス(ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及びピコリン酸を用い、実施例68と同様にして合成し、表題
10 化合物を淡黄色固体として得た。

^1H NMR (DMSO-d₆) δ : 7.18-7.62 (6H, m), 7.92 and 7.99 (total 1H, each dt, $J=8.0, 1.8$ Hz), 8.10-8.44 (5H, m), 8.66-8.72 (1H, m)
ESI-MS (m/e): 416, 418 [M+H]

15

実施例118

5-メチル-2-ピリジン-2-イル-4, 6-ビス-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

ケミカル アンド ファーマスーティカル ブルティン (Chemical and Pharmaceutical Bulletin)、1982年
20 第30巻、10号、3530頁-3543頁に記載されている方法にて合成した2, 4-ジフルオロ-3-メチルニトロベンゼンを用いて、実施例117と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

25 ^1H NMR (DMSO-d₆) δ : 2.03 and 2.10 (total 3H, each s), 7.01-7.50 (6H, m), 7.88 and 7.87 (total 1H, each dt, $J=7.7, 1.6$ Hz), 8.06-8.41 (5H, m), 8.63-8.70 (1H, m)
ESI-MS (m/e): 396 [M+H]

実施例 119

5-フルオロ-2-ピリジン-2-イル-4, 6-ビス-(ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 5 [1, 2, 3]-トリフルオロ-4-ニトロベンゼンを用いて、実施例 117と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (DMSO- d_6) δ : 7.21-7.63 (6H, m), 7.90-8.01 (1H, m), 8.12-8.39 (3H, m), 8.43-8.50 (2H, m), 8.63-8.73 (1H, m)
 10 ESI-MS (m/e): 400 [M+H]

実施例 120

4-(2-シアノフェノキシ)-6-(4-N, N-ジメチルカルバモイルフェニルスルホニル)-2-ピリジン-2-イル-1H-ベンズイミダゾール

(工程 1)

5-(4-カルボキシーフェニルスルファニル)-3-(2-シアノフェノキシ)-2-ニトロフェニルアミンの合成

- 20 実施例 78 で得られた 3-(2-シアノフェノキシ)-5-フルオロ-2-ニトロフェニルアミン 47 mg のジメチルホルムアミド 2 ml 溶液に、4-メルカプト安息香酸 31 mg、及び炭酸カリウム 55 mg を加え、反応液を 60 度にて 2 時間攪拌した。反応液を濃縮し、残渣にトリフルオロ酢酸 1 ml を加え、溶媒を減圧留去した。得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を橙色固体として得た。

(工程 2)

3-(2-シアノフェノキシ)-5-(4-N, N-ジメチルカルバモイルフェニルスルファニル)-2-ニトロフェニルアミンの合成

5 5- (4-カルボキシフェニルスルファニル) - 3- (2-シアノフェノキシ) - 2-ニトロフェニルアミン 40 mg のジクロロメタン 2 ml 溶液に、ジメチルアミン (2.0 M テトラヒドロフラン溶液) 0.059 ml、及び 1-エチル-3- (3'-ジメチルアミノプロピル) -カルボジイミド塩酸塩 28 mg, N-ヒドロキシベンゾトリアゾール水和物 20 mg を加え、反応液を室温にて 1 時間半撹拌した。反応液を、クロロホルムにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=1 5/1) にて精製し、表題化合物を黄色粉末として得た。

(工程 3)

3- (2-シアノフェノキシ) - 5- (4-N, N-ジメチルカルバモイルフェニルスルファニル) -ベンゼン-1, 2-ジアミンの合成

15 3- (2-シアノフェノキシ) - 5- (4-N, N-ジメチルカルバモイルフェニルスルファニル) - 2-ニトロフェニルアミン 32 mg のイソプロピルアルコール 2 ml 溶液に、電解鉄粉 19 mg、及び飽和塩化アンモニウム水溶液 0.2 ml を加え、反応液を 2 時間加熱還流した。触媒の濾去、及び溶媒留去後、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=1 0/1) にて精製し、表題化合物を白色固体として得た。

(工程 4)

3- (2-シアノフェノキシ) - 5- (4-N, N-ジメチルカルバモイルフェニルスルホニル) -ベンゼン-1, 2-ジアミンの合成

25 3- (2-シアノフェノキシ) - 5- (4-N, N-ジメチルアミノカルボニルフェニルスルファニル) -ベンゼン-1, 2-ジアミン 25 mg のジクロロメタン 2 ml 溶液に、メタクロロ過安息香酸 38 mg を加え、反応液を室温にて 15 分間撹拌した。反応液を、クロロホルムにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 6

0 F₂₅₄、Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を黄色粉末として得た。

(工程5)

4-(2-シアノフェノキシ)-6-(4-N, N-ジメチルアミノカルボニルフェニルスルホニル)-2-(ピリジン-2-イル)-1H-ベンズイミダゾールの製造

3-(2-シアノフェノキシ)-5-(4-N, N-ジメチルアミノカルボニルフェニルスルホニル)-ベンゼン-1, 2-ジアミンを用いて、実施例67 (工程4) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

¹H NMR (CDCl₃) δ: 2.91 and 2.92 (total 3H, each s), 3.10 (3H, s), 6.99 (1H, m), 7.23-7.30 (1H, m), 7.39-7.46 (2H, m), 7.50-7.58 (3H, m), 7.68-7.78 (1H, m), 7.75 and 8.33 (total 1H, each s), 7.85 and 7.92 (total 1H, each t, J=8.4 Hz), 7.95-8.20 (2H, m), 8.39 and 8.42 (total 1H, each d, J=8.4 Hz), 8.63-8.67 (1H, m)

ESI-MS (m/e): 524 [M+H]

20

実施例121

1-(2-(6-(4-オキサゾール-5-イルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

25 (工程1)

3-ブロモ-4-メトキシメトキシ安息香酸 エチルエステルの合成

Monatsh. Chem.; 22; 1901; 437に記載されている方法にて合成した3-ブロモ-4-ヒドロキシ安息香酸 エチルエステル 20.5 g のテトラヒドロフラン300 ml 溶液に、氷冷下、水素化ナトリウ

- ム 5. 5 g を加え、反応液を 30 分間攪拌した後、同温にて反応液にクロロメ
チルメチルエーテル 10 ml を加え、反応液を室温にて一終夜攪拌した。反応
液を酢酸エチルにて希釈し、水にて洗浄した後、水層を酢酸エチルにて抽出し、
無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた固体をヘキ
5 サンに懸濁させて濾取し、表題化合物を白色固体として得た。

(工程 2)

2 - (5 - エトキシカルボニル - 2 - メトキシメトキシーフェニル) - ピ
ロール - 1 - カルボン酸 t - ブチルエステルの合成

- 3 - プロモ - 4 - メトキシメトキシ安息香酸 エチルエステル 21 g のジメ
10 トキシエタン 350 ml 溶液に、1 - (t - ブトキシカルボニル) ピロール -
2 - ボロン酸 21 g、テトラキストリフェニルホスフィンパラジウム 4. 2 g、
炭酸ナトリウム水溶液 (2 M) 153 ml を順次加え、反応液を窒素雰囲気下、
一終夜加熱環流した。冷却後、反応液を水にて希釈、クロロホルムにて抽出し、
無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリ
15 カゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル = 12/
1 ~ 10/1) により精製し、表題化合物を白色固体として得た。

(工程 3)

2 - (5 - エトキシカルボニル - 2 - メトキシメトキシーフェニル) - ピロ
リジン - 1 - カルボン酸 t - ブチルエステルの合成

- 20 2 - (5 - エトキシカルボニル - 2 - メトキシメトキシーフェニル) - ピ
ロール - 1 - カルボン酸 t - ブチルエステル 28. 4 g のエタノール 400
ml 溶液に 5 % 白金炭素触媒 8. 2 g を加え、反応液を水素雰囲気下、3 日間
攪拌した。触媒をセライトにて濾去後、溶媒を減圧留去し、得られた残渣をシ
リカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル = 1/
25 6. 5 ~ 1/6) により精製し、表題化合物を無色油状物質として得た。

(工程 4)

3 - (1 - アセチル - ピロリジン - 2 - イル) - 4 - ヒドロキシ安息香酸
エチルエステルの合成

2 - (5 - エトキシカルボニル - 2 - メトキシメトキシーフェニル) - ピロ

リジン-1-カルボン酸 t-ブチルエステル 26 g のエタノール 250 ml
と水 50 ml の混合溶液に、p-トルエンスルホン酸一水和物 13 g を加え、
反応液を 2 日間加熱還流した。冷却後、反応液を水にて希釈し、重曹水にて中
和、クロロホルム/メタノール混合溶媒 (10/1) にて抽出し、無水硫酸マ
グネシウムにて乾燥した。溶媒を減圧留去し、粗生成物を得た。得られた粗生
5 成物のピリジン 200 ml 溶液に、無水酢酸 13 ml を加えて攪拌した。1 時
間後、無水酢酸 6 ml を加えた。さらに 1 時間後ピリジン 150 ml を加え、
さらに 40 分後トリエチルアミン 5 ml を加えた。さらに 30 分後無水酢酸 3
ml を加え、さらに反応液を 30 分間攪拌した。反応液を酢酸エチルにて希釈
10 し、飽和重曹水にて洗浄、水層を酢酸エチルにて抽出した。合わせた有機層を
無水硫酸マグネシウムにて乾燥後、溶媒を減圧留去し、粗生成物を得た。得ら
れた粗生成物のメタノール 200 ml 溶液に、炭酸カリウム 10 g を加え、反
応液を 4 時間室温にて攪拌した。反応液を減圧留去し、得られた残渣を飽和塩
化アンモニウム水溶液にて希釈、酢酸エチルにて抽出した。無水硫酸マグネシ
15 ウムにて乾燥後、溶媒を減圧留去し、得られた固体を酢酸エチルにて濾取する
ことにより、表題化合物を白色固体として得た。

(工程 5)

3-(1-アセチル-ピロリジン-2-イル)-4-ベンジルオキシ安息香
酸 エチルエステルの合成

20 3-(1-アセチル-ピロリジン-2-イル)-4-ヒドロキシ安息香酸
エチルエステル 12.4 g のジメチルホルムアミド 100 ml 溶液に、炭酸カ
リウム 15 g、臭化ベンジル 6.4 ml を加え、反応液を 50 度にて 1 時間攪
拌した。反応液を冷却後、飽和塩化アンモニウム水溶液にて希釈し、酢酸エチ
ルにて抽出した。有機層を水にて洗浄後、無水硫酸マグネシウムにて乾燥した。
25 溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展
開溶媒: ヘキサン/酢酸エチル = 10/1 ~ 1/2 ~ 1/3) により精製し、
表題化合物を黄色油状物質として得た。

(工程 6)

3-(1-アセチル-ピロリジン-2-イル)-4-ベンジルオキシ安息香

酸の合成

3 - (1 - アセチル - ピロリジン - 2 - イル) - 4 - ベンジルオキシ安息香酸 エチルエステル 18.7 g のエタノール 200 ml 溶液に 4 規定水酸化ナトリウム水溶液 23 ml を加え、反応液を室温にて一終夜撹拌した。さらに、
5 反応液に 4 規定水酸化ナトリウム水溶液 15 ml を加え、反応液を 7 時間撹拌した。反応溶媒を減圧留去し、得られた残渣を水にて希釈、エーテルにて洗浄した。水層を 6 規定塩酸にて酸性にした後、クロロホルムにて抽出し、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、表題化合物を白色固体として得た。

10 (工程 7)

(3 - (1 - アセチル - ピロリジン - 2 - イル) - 4 - ベンジルオキシフェニル) - カルバミン酸 t - ブチルエステルの合成

3 - (1 - アセチル - ピロリジン - 2 - イル) - 4 - ベンジルオキシ安息香酸 5 g のトルエン 15 ml と 2 - メチル - 2 - プロパノール 15 ml の混合溶
15 液に、ジイソプロピルエチルアミン 3.0 ml、アジ化ジフェニルホスホリル 3.8 ml を順次加え、反応液を一終夜加熱還流した。冷却後、反応液に飽和食塩水と飽和重曹水を加え、酢酸エチルにて抽出し、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル = 1／0 ~ 1／1 ~ 0／1）によ
20 り精製し、表題化合物を無色アモルファスとして得た。

(工程 8)

1 - (2 - (4, 5 - ジアミノ - 2 - ベンジルオキシフェニル) - ピロリジン - 1 - イル) - エタノンの合成

(3 - (1 - アセチル - ピロリジン - 2 - イル) - 4 - ベンジルオキシフェニル) - カルバミン酸 t - ブチルエステル 4.1 g のトリフルオロ酢酸
25 50 ml 溶液に、硝酸カリウム 1.1 g を加えて、反応液を室温にて一終夜撹拌した。反応溶媒を減圧留去し、得られた残渣に氷水を加えた後、アンモニア水にて中和し、酢酸エチルにて希釈した。沈殿物を濾取し、粗生成物を茶色固体として得た。濾液を飽和塩化ナトリウム水溶液にて希釈し、酢酸エチルにて

抽出後、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：酢酸エチル）により精製し、得られた固体を酢酸エチルにて懸濁させて濾取し、粗生成物を茶色固体として得た。得られた粗生成物 2.8 g のエタノール 100 ml 溶液に、ヒド
5 ラジーン水和物 1.5 ml、展開ラネーニッケル触媒 1 g を順次加え、反応液を室温にて 3 時間攪拌した。触媒をセライトにより濾去し、溶媒を減圧留去した。得られた残渣を飽和重曹水にて希釈し、酢酸エチルにて抽出後、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカ
10 ラムクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝100／0～99／1～98／2～97／3～96／4～93／7）により精製し、表題化合物を緑色アモルファスとして得た。

（工程 9）

1-（2-（6-ベンジルオキシ-2-ピリジン-2-イル-3-（2-トリメチルシリニル-エトキシメチル）-3H-ベンズイミダゾール-5-イ
15 ル）-ピロリジン-1-イル）-エタノンの合成

1-（2-（4,5-ジアミノ-2-ベンジルオキシフェニル）-ピロリジン-1-イル）-エタノン 1.39 g のトルエン 43 ml 溶液に、ピリジン-2-カルボキサアルデヒド 460 mg のトルエン溶液 3 ml を加え、反応液を室温にて攪拌した。2 時間後、ピリジン-2-カルボキサアルデヒド 46
20 mg を加え、反応液を 90 度にて 2 時間攪拌した。さらに、ピリジン-2-カルボキサアルデヒド 46 mg を加え、反応液を 90 度にて 10 時間攪拌した。冷却後、析出した固体を濾取し、粗生成物を茶色固体として得た。得られた粗生成物 1.1 g のテトラヒドロフラン 20 ml 溶液に、水素化ナトリウム 144 mg、2-（クロロメトキシ）エチルトリメチルシラン 667 mg を加え、
25 反応液を室温にて 2.5 時間攪拌した。反応液に飽和重曹水を加え、酢酸エチルにて抽出し、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：酢酸エチル）により精製し、表題化合物を茶色アモルファスとして得た。

（工程 10）

1- (2- (6-ヒドロキシ-2-ピリジン-2-イル-3- (2-トリメチルシラニル-エトキシメチル) -3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -エタノンの合成

- 1- (2- (6-ベンジルオキシ-2-ピリジン-2-イル-3- (2-トリメチルシラニル-エトキシメチル) -3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -エタノン 1. 18 g のエタノール 20 ml 溶液に、ギ酸アンモニウム 713 mg、20%水酸化パラジウム-炭素触媒 119 mg を加え、反応液を 5 時間加熱還流した。反応液にギ酸アンモニウム 157 mg、20%水酸化パラジウム-炭素触媒 56 mg を加え、さらに反応液を 1 時間加熱還流した。冷却後、触媒をセライトにより濾去し、溶媒を減圧留去した。得られた残渣を 1 規定塩酸にて希釈し、酢酸エチルに抽出後、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム/メタノール=100/0~99/1~98/2）により精製し、表題化合物を茶色アモルファスとして得た。

（工程 11）

- 1- (2- (6- (4-オキサゾール-5-イル-フェノキシ) -2-ピリジン-2-イル-3- (2-トリメチルシラニル-エトキシメチル) -3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -エタノンの合成
- 1- (2- (6-ヒドロキシ-2-ピリジン-2-イル-3- (2-トリメチルシラニル-エトキシメチル) -3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -エタノン 29 mg のピリジン 1 ml 溶液に、5- (4-ブロモフェニル) -オキサゾール 30 mg、炭酸セシウム 56 mg、酸化銅 (II) 15 mg を加え、反応液を封管中 120 度にて一終夜攪拌した。冷却後、反応液に飽和塩化アンモニウム水溶液、飽和食塩水を順次加え、酢酸エチルにて抽出し、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=12/1) にて精製し、表題化合物を黄色油状物質として得た。

(工程 12)

1 - (2 - (6 - (4 - オキサゾール - 5 - イル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノンの製造

- 5 1 - (2 - (6 - (4 - オキサゾール - 5 - イル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 - (2 - トリメチルシラニル - エトキシメチル) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン 24 mg をトリフルオロ酢酸 1 ml に溶解し、反応液を室温にて 2 時間攪拌した。溶媒を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー (ODS -
- 10 AS - 360 - CC (YMC 社製) 移動相: 水 - アセトニトリル - 0.1% トリフルオロ酢酸) にて精製し、表題化合物を黄色油状物質として得た。
- $^1\text{H NMR}$ (CDCl_3) δ : 1.73 - 2.69 (7H, m), 3.54 - 3.91 (2H, m), 5.21 - 5.48 (1H, m), 6.91 - 7.98, 8.30 - 8.51, 8.57 - 8.73 (13H, each m)
- 15 ESI-MS (m/e): 466 [M+H]

実施例 122

3 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - ベンゾニトリル

- 20 実施例 121 (工程 10) で得られた 1 - (2 - (6 - ヒドロキシ - 2 - ピリジン - 2 - イル - 3 - (2 - トリメチルシラニル - エトキシメチル) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、及び 3 - シアノプロモベンゼンを用いて、実施例 121 (工程 11)、(工程 12) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。
- 25

$^1\text{H NMR}$ (CDCl_3) δ : 1.80 - 2.42 (7H, m), 3.56 - 3.93 (2H, m), 5.14 - 5.45 (1H, m), 6.91 - 7.73 (7H, m), 7.80 - 7.96 (1H, m), 8.30 - 8.43 (1H, m), 8.58 - 8.70 (1H, m), 10.58 - 10.82 (1H,

m)

ESI-MS (m/e) : 424 [M+H]

実施例123

5 3-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンズアミド

実施例122で得られた3-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンゾニトリルを用いて、実施例43と同様の方法、これに準じた方法
10 又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl₃) δ : 1.70-2.39 (7H, m), 3.39-3.89 (2H, m), 5.17-6.24 (3H, m), 6.97-7.92 (8H, m), 8.26-8.42 (1H, m), 8.52-8.67 (1H, m), 10.42-10.72 (1H, m)

15 ESI-MS (m/e) : 442 [M+H]

実施例124

5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-カルボニ
20 トリル

5-ブロモ-ピリジン-2-カルボニトリルを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl₃) δ : 1.50-2.42 (7H, m), 3.56-3.88 (2H, m), 5.09-5.40 (1H, m), 6.89-7.92 (6H, m), 8.26-8.70 (3H, m), 10.63-11.05 (1H, m)

ESI-MS (m/e) : 425 [M+H]

実施例 125

5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-カルボン酸アミド

- 5 実施例 124 で得られた 5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-カルボニトリルを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

- 10 $^1\text{H NMR}$ (CDCl_3) δ : 0.60-2.42 (7H, m), 3.42-3.90 (2H, m), 4.99-5.80 (2H, m), 6.74-8.67 (10H, m), 10.42-10.85 (1H, m)
ESI-MS (m/e): 443 [M+H]

- 15 実施例 126-1、126-2

1-(2-(6-(5-ブロモ-ピリジン-2-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- 1-(2-(6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン
- 20

5-ブロモ-2-メタンスルホニル-ピリジンを用いて、実施例 122 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をそれぞれ得た。

- 25 1-(2-(6-(5-ブロモ-ピリジン-2-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

$^1\text{H NMR}$ (CDCl_3) δ : 1.50-2.40 (7H, m), 3.50-3.87 (2H, m), 5.03-5.14, 5.31-5.42 (1H, eac

h m), 6.71-7.88, 10.48-11.15 (7H, each m), 8.08-8.40 (2H, m), 8.50-8.69 (1H, m)

ESI-MS (m/e) : 478, 480 [M+H]

1- (2- (6- (6-メタンスルホニル-ピリジン-3-イルオキシ) -
5 2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) -ピロリジ
ン-1-イル) -エタノン

¹HNMR (CDCl₃) δ : 1.57-2.59 (7H, m), 3.08-3.
27 (3H, m), 3.57-3.89 (2H, m), 5.14-5.40
(1H, m), 6.94-7.64 (4H, m), 7.82-8.15 (2H,
10 m), 8.33-8.75 (3H, m)

ESI-MS (m/e) : 478 [M+H]

実施例127

1- (2- (2-ピリジン-2-イル-6- (キノリン-6-イルオキシ) -
15 3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -エタノン

6-ブロモ-キノリンを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

¹HNMR (CDCl₃) δ : 1.67-2.69 (7H, m), 3.40-4.
20 04 (2H, m), 5.25-5.63 (1H, m), 6.80-9.13
(12H, m), 10.22-11.44 (1H, br)

ESI-MS (m/e) : 450 [M+H]

実施例128

25 4- (6- (1-アセチル-ピロリジン-2-イル) -2-ピリジン-2-イ
ル-1H-ベンズイミダゾール-5-イルオキシ) -2-メチル-ベンゾニト
リル

4-ブロモ-2-メチル-ベンゾニトリルを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題

化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.48–2.54 (10H, m), 3.20–3.89 (2H, m), 5.06–5.41 (1H, m), 6.80–8.87 (10H, m)

5 ESI-MS (m/e): 438 [M+H]

実施例129

1 – (2 – (2 – ピリジン – 2 – イル – 6 – (4 – トリフルオロメトキシ –
 フェノキシ) – 3H – ベンズイミダゾール – 5 – イル) – ピロリジン – 1 – イ
 10 ル) – エタノン

1 – ブロモ – 4 – トリフルオロメトキシ – ベンゼンを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.43–2.69 (7H, m), 3.32–3.91 (2H, m), 5.20–5.59 (1H, m), 6.23–8.97 (11H, m)

ESI-MS (m/e): 483 [M+H]

実施例130

20 1 – (2 – (2 – ピリジン – 2 – イル – 6 – (キノリン – 3 – イルオキシ) –
 3H – ベンズイミダゾール – 5 – イル) – ピロリジン – 1 – イル) – エタノン

3 – ブロモ – キノリンを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 1.00–2.47 (7H, m), 3.37–4.00 (2H, m), 5.26–5.54 (1H, m), 6.98–9.10 (12H, m), 10.44–10.73 (1H, m)

ESI-MS (m/e): 450 [M+H]

実施例 131

1 - (2 - (6 - (4 - アセチル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン

1 - (4 - ヨード - フェニル) - エタノンを用いて、実施例 122 と同様の
5 方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.47 - 2.60 (10H, m), 3.52 - 3.88 (2H, m), 5.12 - 5.41 (1H, m), 6.97 - 7.74 (6H, m), 7.80 - 8.02 (3H, m), 8.30 - 8.44 (1
10 H, m), 8.57 - 8.70 (1H, m)

ESI-MS (m/e): 441 [M+H]

実施例 132

1 - (2 - (6 - (ビフェニル - 4 - イルオキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタ
15 ノン

4 - ブロモ - ビフェニルを用いて、実施例 122 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 1.13 - 2.47 (7H, m), 3.40 - 3.91 (2H, m), 5.20 - 5.60 (1H, m), 6.72 - 7.89 (13H, m), 8.25 - 8.42 (1H, m), 8.42 - 8.67 (1H, m), 10.29 - 10.60 (1H, m)

ESI-MS (m/e): 475 [M+H]

25

実施例 133

4 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - N, N - ジメチル - ベン
ゼンスルホンアミド

4-ヨード-N, N-ジメチル-ベンゼンスルホンアミドを用いて、実施例 1 2 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.50–3.00 (13H, m), 3.40–3.92 (2H, m), 5.14–5.50 (1H, m), 6.40–8.80 (11H, m)

ESI-MS (m/e): 506 [M+H]

実施例 1 3 4

10 1-(2-(6-(ビフェニル-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

3-ブロモ-ビフェニルを用いて、実施例 1 2 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

15 $^1\text{H NMR}$ (CDCl_3) δ : 0.80–2.50 (7H, m), 3.40–3.91 (2H, m), 5.20–5.60 (1H, m), 6.80–7.95 (13H, m), 8.25–8.45 (1H, m), 8.50–8.70 (1H, m)

ESI-MS (m/e): 475 [M+H]

20

実施例 1 3 5

1-(2-(6-(4-(プロパン-2-スルホニル)-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

25 1-ヨード-4-(プロパン-2-スルホニル)-ベンゼンを用いて、実施例 1 2 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.10–2.50 (13H, m), 3.05–3.30 (1H, m), 3.50–3.95 (2H, m), 5.05–5.5

0 (1H, m), 7.00–7.95 (8H, m), 8.30–8.50 (1H, m), 8.58–8.75 (1H, m), 10.60–10.95 (1H, m)

ESI-MS (m/e) : 505 [M+H]

5

実施例136

4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-2-トリフルオロメチル-ベンゾニトリル

- 10 4-ブロモ-2-トリフルオロメチル-ベンゾニトリルを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CDCl₃) δ : 1.10–2.45 (7H, m), 3.50–3.95 (2H, m), 5.00–5.45 (1H, m), 6.60–7.95 (7H, m), 8.30–8.45 (1H, m), 8.55–8.75 (1H, m), 10.80–11.60 (1H, m)

15 ESI-MS (m/e) : 492 [M+H]

実施例137-1、137-2

- 20 4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-2-トリフルオロメチル-ベンズアミド・トリフルオロ酢酸塩

- 4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-N-エチル-2-トリフルオロメチル-ベンズアミド・トリフルオロ酢酸塩
- 25

実施例136で得られた4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-2-トリフルオロメチル-ベンゾニトリルを用いて、実施例43、及び実施例121(工程12)と同様の方法、これに準じた方法又はこれらと常法

とを組み合わせることにより、表題化合物をそれぞれ得た。

4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-2-トリフルオロメチル-ベンズアミド・トリフルオロ酢酸塩

- 5 $^1\text{H NMR}$ (CD_3OD) δ : 1.05-2.80 (7H, m), 3.50-4.20 (2H, m), 5.30-5.45 (1H, m), 7.30-7.80 (6H, m), 8.05-8.20 (1H, m), 8.20-8.38 (1H, m), 8.80-8.90 (1H, m)

ESI-MS (m/e): 510 $[\text{M}+\text{H}]$

- 10 4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-N-エチル-2-トリフルオロメチル-ベンズアミド・トリフルオロ酢酸塩

- $^1\text{H NMR}$ (CD_3OD) δ : 1.05-2.80 (10H, m), 3.60-4.05 (2H, m), 4.80-5.00 (2H, m), 5.30-5.45 (1H, m), 7.30-7.80 (5H, m), 8.05-8.20 (1H, m), 8.20-8.38 (1H, m), 8.80-8.90 (1H, m), 9.10-9.30 (1H, m)

ESI-MS (m/e): 538 $[\text{M}+\text{H}]$

- 20 実施例138

1-(2-(6-(4-(2-ジメチルアミノ-エトキシ)-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- (2-(4-ヨード-フェノキシ)-エチル)-ジメチルアミンを用いて、
25 実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.05-2.90 (13H, m), 3.00-4.45 (6H, m), 5.20-5.45 (1H, m), 6.80-8.00 (8H, m), 8.25-8.40 (1H, m), 8.50-8.80 (1

H, m)

ESI-MS (m/e) : 486 [M+H]

実施例139

- 5 1-(2-(6-(4-ヒドロキシメチルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- 4-ブロモベンジルアルコールを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を
10 白色固体として得た。

$^1\text{H NMR}$ (CDCl₃) δ : 1.68-2.40 (7H, m), 3.53-3.88 (2H, m), 4.62-4.72 (2H, m), 5.22-5.56 (1H, m), 6.82-7.62 (7H, m), 7.80-7.89 (1H, m), 8.32-8.40 (1H, m), 8.55-8.64 (1H, m)

- 15 ESI-MS (m/e) : 429 [M+H]

実施例140

- 4-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-N,N-ジメチルベン
20 ズアミド

4-ブロモ安息香酸 ジメチルアミドを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- $^1\text{H NMR}$ (CDCl₃) δ : 1.81-2.40 (7H, m), 2.98-3.17 (6H, m), 3.56-3.87 (2H, m), 5.20-5.53 (1H, m), 6.93-7.65 (7H, m), 7.81-7.89 (1H, m), 8.33-8.41 (1H, m), 8.60-8.67 (1H, m)

ESI-MS (m/e) : 470 [M+H]

実施例 141

4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-N-メチル-ベンズアミド

- 5 4-ブロモ-N-メチルベンズアミドを用いて、実施例 122 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80–2.39 (4H, m), 1.84 and 2.16 (total 3H, each s), 2.98–3.02 (3H, m), 3.58–3.74 (1H, m), 3.78–3.87 (1H, m), 5.16–5.43 (1H, m), 6.74–7.89 (8H, m), 8.36–8.39 (1H, m), 8.63–8.66 (1H, m)

ESI-MS (m/e): 456 [M+H]

15 実施例 142

1-(2-(2-ピリジン-2-イル-6-(4-(ピロリジン-1-カルボニル)-フェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- 20 (4-ブロモ-フェニル)-ピロリジン-1-イル-メタノンを用いて、実施例 122 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80–2.40 (8H, m), 1.87 and 2.21 (total 3H, each s), 3.43–3.52 (2H, m), 3.60–3.71 (3H, m), 3.81–3.90 (1H, m), 5.21–5.50 (1H, m), 6.84–7.02 (2H, m), 7.25–7.58 (5H, m), 7.83–7.93 (1H, m), 8.36–8.45 (1H, m), 8.62–8.67 (1H, m)

ESI-MS (m/e): 496 [M+H]

実施例 143

1 - (2 - (6 - (4 - (モルホリン - 4 - カルボニル) - フェノキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
ン - 1 - イル) - エタノン

- 5 (4 - ブロモ - フェニル) - モルホリン - 4 - イル - メタノンを用いて、実施例 122 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.78 - 2.62 (7H, m), 3.40 - 3.90 (10H, m), 5.23 - 5.50 (1H, m), 6.82 - 7.54
 10 (7H, m), 7.86 - 7.94 (1H, m), 8.38 - 8.46 (1H, m), 8.64 - 8.69 (1H, m)

ESI-MS (m/e): 512 [M+H]

実施例 144

- 15 4 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イルオキシ) 安息香酸・トリフルオロ酢酸塩

- 4 - ブロモ - 安息香酸を用いて、実施例 122 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。
 20

$^1\text{H NMR}$ (CDCl_3) δ : 1.86 and 2.10 (total 3H, each s), 1.92 - 2.48 (4H, m), 3.41 - 3.90 (2H, m), 5.36 - 5.39 (1H, m), 7.13 - 7.72 (5H, m), 8.00 - 8.07 (3H, m), 8.22 - 8.26 (1H, m), 8.7
 25 3 - 8.80 (1H, m)

ESI-MS (m/e): 443 [M+H]

実施例 145

1 - (2 - (6 - (4 - (ピペリジン-1-カルボニル) - フェノキシ) -
2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) - ピロリジ
ン-1-イル) - エタノン

(4-ブロモ-フェニル) - ピペリジン-1-イル-メタノンを用いて、実
 5 施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ
 ることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.45-2.40 (10H, m), 1.88 a
 nd 2.20 (total 3H, each s), 3.30-3.90 (6H,
 m), 5.23-5.53 (1H, m), 6.83-7.55 (7H, m),
 10 7.84-7.94 (1H, m), 8.37-8.46 (1H, m), 8.6
 3-8.68 (1H, m)

ESI-MS (m/e): 510 [M+H]

実施例146

15 1 - (2 - (6 - (4 - (4-アセチル-ピペラジン-1-カルボニル) -
フェノキシ) - 2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イ
ル) - ピロリジン-1-イル) - エタノン

1 - (4 - (4-プロモ-ベンゾイル) - ピペラジン-1-イル) - エタノ
 ンを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法
 20 とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.84-2.40 (10H, m), 3.24-
 3.88 (10H, m), 5.22-5.48 (1H, m), 6.94-7.
 09 (2H, m), 7.22-7.48 (5H, m), 7.84-7.93
 (1H, m), 8.37-8.43 (1H, m), 8.63-8.66 (1H,
 25 m)

ESI-MS (m/e): 553 [M+H]

実施例147

4 - (6 - (1-アセチル-ピロリジン-2-イル) - 2-ピリジン-2-イ

ル-1H-ベンズイミダゾール-5-イルオキシ)-ベンゾニトリル

(工程1)

4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミ
5 ダゾール-5-イルオキシ)-ベンゾニトリルの合成

実施例121(工程10)で得られた1-(2-(6-ヒドロキシ-2-ピ
リジン-2-イル-3-(2-トリメチルシラニル-エトキシメチル)-3
H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン3
0mg、及び4-フルオロシアノベンゼン20mgのN-メチル-ピロリジノ
10 ン1ml溶液に、水素化ナトリウム5.8mgを加え、反応液を封管中100
度にて一終夜攪拌した。冷却後、反応液に飽和重曹水を加え、酢酸エチルにて
抽出し、有機層を水にて洗浄、無水硫酸マグネシウムにて乾燥した。溶媒を減
圧留去し、得られた残渣を分取用薄層クロマトグラフィー(Kieselge
1TM60F₂₅₄、Art5744(メルク社製)、クロロホルム/メタノール=
15 9/1)にて精製し、表題化合物を黄色油状物質として得た。

(工程2)

4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンゾニトリルの製造

4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミ
20 ダゾール-5-イルオキシ)-ベンゾニトリルを用いて、実施例121(工程
12)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を油状物質として得た。

¹HNMR(CDC1₃) δ: 1.52-2.42(7H, m), 3.42-3.
25 92(2H, m), 5.02-5.40(1H, m), 6.77-7.75
(7H, m), 7.75-7.94(1H, m), 8.20-8.46(1H,
m), 8.50-8.69(1H, m), 10.67-11.06(1H,
m)

ESI-MS(m/e): 424[M+H]

実施例 148

4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンズアミド

- 5 実施例 147 で得られた 4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンゾニトリルを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.05-2.40 (7H, m), 3.43-3.89 (2H, m), 5.10-6.32 (3H, m), 6.88-7.90 (8H, m), 8.27-8.42 (1H, m), 8.53-8.68 (1H, m), 10.47-11.80 (1H, m)
ESI-MS (m/e): 442 [M+H]

15 実施例 149

2-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンゾニトリル

- 20 2-フルオロ-ベンゾニトリルを用いて、実施例 147 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.50-2.49 (7H, m), 3.43-3.89 (2H, m), 5.10-5.34 (1H, m), 6.83-7.92 (8H, m), 8.31-8.42 (1H, m), 8.53-8.68 (1H, m), 10.80-11.23 (1H, m)
25 ESI-MS (m/e): 424 [M+H]

実施例 150

2-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンズアミド

実施例 149 で得られた 2-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ベンゾニトリルを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として
5 得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.52-2.46 (7H, m), 3.43-3.91 (2H, m), 5.10-5.51 (1H, m), 5.99 (1H, br s), 6.72-7.98 (8H, m), 8.26-8.43 (2H, m), 8.59-8.70 (1H, m), 10.58-10.94 (1H, m)

10 ESI-MS (m/e): 442 [$\text{M}+\text{H}$]

実施例 151

1-(2-(6-(4-ニトロ-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

15 4-フルオロ-ニトロベンゼンを用いて、実施例 147 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.40-2.50 (7H, m), 3.50-3.95 (2H, m), 5.05-5.40 (1H, m), 7.00-7.80 (5H, m), 7.80-7.95 (1H, m), 8.15-8.30 (2H, m), 8.30-8.45 (1H, m), 8.60-8.70 (1H, m), 10.60-11.00 (1H, m)

ESI-MS (m/e): 444 [$\text{M}+\text{H}$]

25 実施例 152

1-(2-(2-ピリジン-2-イル-6-(4-(2H-テトラゾール-5-イル)-フェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

実施例 147 (工程 1) で得られた 4-(6-(1-アセチル-ピロリジ

ン-2-イル)-2-ピリジン-2-イル-1-(2-トリメチルシラニル-
 エトキシメチル)-1H-ベンズイミダゾール-5-イルオキシ)-ベンズニ
 トリルを用いて、実施例60、及び実施例121(工程12)と同様の方法、
 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
 5 を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.51-2.58 (7H, m), 3.43-3.
 90 (2H, M), 5.09-5.55 (1H, m), 6.73-7.60,
 7.69-8.04, 8.29-8.69 (10H, each m)

ESI-MS (m/e): 467 [M+H]

10

実施例153

1-(2-(6-(4-(5-メチル-[1, 2, 4]オキサジアゾール-
 3-イル)-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダ
 ゴール-5-イル)ピロリジン-1-イル)-エタノン

15 実施例147(工程1)で得られた4-(6-(1-アセチル-ピロリジ
 ン-2-イル)-2-フェニル-1-(2-トリメチルシラニル-エトキシメ
 チル)-1H-ベンズイミダゾール-5-イルオキシ)-ベンズニトリルを用
 いて、実施例61、実施例64及び実施例121(工程12)と同様の方法、
 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
 20 を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.49-2.7 (10H, m), 3.39-3.
 90 (2H, m), 5.17-5.52 (1H, m), 6.26-8.89
 (11H, m)

ESI-MS (m/e): 481 [M+H]

25

実施例154

3-(4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-
 2-イル-1H-ベンズイミダゾール-5-イルオキシ)-フェニル)-4
 H-[1, 2, 4]オキサジアゾール-5-オン

実施例 147 (工程 1) で得られた 4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミダゾール-5-イルオキシ)-ベンゾニトリルを用いて、実施例 61、実施例 62、及び実施例 121 (工程 12) と
 5 同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.82-2.47 (7H, m), 3.60-3.94 (2H, m), 5.24-5.43 (1H, m), 7.15-8.05 (8H, m), 8.23-8.31 (1H, m), 8.71-8.78 (1
 10 H, m)

ESI-MS (m/e): 483 [M+H]

実施例 155

5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-1,3-ジヒドロベンズイミダゾール-2-オン
 15

(工程 1)

1-(2-(6-(3,4-ジニトロフェノキシ)-2-ピリジン-2-イル-3-(2-トリメチルシラニル-エトキシメチル)-3H-ベンズイミ
 20 ダゾール-5-イル)-ピロリジン-1-イル)-エタノンの合成

4-フルオロ-1,2-ジニトロベンゼンを用いて、実施例 147 (工程 1) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を赤色油状物質として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.80-2.57 (7H, m), 3.61-4.02 (2H, m), 5.27-5.60 (1H, m), 6.77-7.60 (6H, m), 7.91-8.06 (1H, m), 8.17-8.33 (1H, m), 8.72 (1H, brs)
 25

ESI-MS (m/e): 455 [M+H]

(工程 2)

1 - (2 - (6 - (3, 4 - ジアミノ - フェノキシ) - 2 - ピリジン - 2 -
イル - 3 - (2 - トリメチルシラニル - エトキシメチル) - 3 H - ベンズイミ
ダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノンの合成

1 - (2 - (6 - (3, 4 - ジニトロ - フェノキシ) - 2 - ピリジン - 2 -
5 イル - 3 - (2 - トリメチルシラニル - エトキシメチル) - 3 H - ベンズイミ
ダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン 7.2 mg のエタ
ノール 1 ml 溶液に、ヒドラジン - 水和物 0.030 ml、展開ラネーニッケ
ル触媒 20 mg を加え、反応液を室温にて 2 時間攪拌した。触媒をセライトに
より濾去し、溶媒を減圧留去した。得られた残渣を分取用薄層クロマトグラ
10 フィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、ク
ロロホルム / メタノール = 9 / 1) にて精製し、表題化合物を茶色油状物質と
して得た。

(工程 3)

5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 -
15 イル - 1 - (2 - トリメチルシラニル - エトキシメチル) - 1 H - ベンズイミ
ダゾール - 5 - イルオキシ) - 1, 3, - ジヒドロ - ベンズイミダゾール -
2 - オンの合成

1 - (2 - (6 - (3, 4 - ジアミノ - フェノキシ) - 2 - ピリジン - 2 -
イル - 3 - (2 - トリメチルシラニル - エトキシメチル) - 3 H - ベンズイミ
20 ダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノンを用いて、実施例
62 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を褐色油状物質として得た。

(工程 4)

5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 -
25 イル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - 1, 3 - ジヒドロ - ベ
ンズイミダゾール - 2 - オンの製造

5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 -
イル - 1 - (2 - トリメチルシラニル - エトキシメチル) - 1 H - ベンズイミ
ダゾール - 5 - イルオキシ) - 1, 3, - ジヒドロ - ベンズイミダゾール - 2

ーオンを用いて、実施例121（工程12）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をアモルファスとして得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80–2.57 (7H, m), 3.61–4.02 (2H, m), 5.27–5.60 (1H, m), 6.77–7.60 (6H, m), 7.91–8.06 (1H, m), 8.17–8.33 (1H, m), 8.72 (1H, brs)

ESI-MS (m/e): 455 [$M+H$]

10 実施例156

1-(2-(6-(3H-ベンズイミダゾール-5-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

実施例155（工程2）で得られた1-(2-(6-(3,4-ジアミノフェノキシ)-2-ピリジン-2-イル-3-(2-トリメチルシラニル-エトキシメチル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン19mgをギ酸1mlに溶解し、反応液を100度にて2時間攪拌した。反応液を減圧下にて濃縮し、得られた残渣を逆相中圧液体クロマトグラフィー（ODS-AS-360-CC（YMC社製）移動相：水-アセトニトリル-0.1%トリフルオロ酢酸）にて精製し、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.80–2.25 (7H, m), 3.60–4.00 (2H, m), 5.33–5.69 (1H, m), 7.00–7.80, 7.91–8.04, 8.16–8.30, 8.67–8.80 (10H, each m)

25 ESI-MS (m/e): 439 [$M+H$]

実施例157

1-(2-(6-(2-メチル-3H-ベンズイミダゾール-5-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピ

ロリジン-1-イル)-エタノン

酢酸を用いて、実施例 156 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.69–2.63 (10H, m), 3.42–3.91 (2H, m), 5.20–5.64 (1H, m), 6.58–7.87 (9H, m) 8.22–8.66 (2H, m)

ESI-MS (m/e) : 453 [M+H]

実施例 158

10 5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリミジン-2-カルボニトリル

5-ブロモ-ピリミジン-2-カルボニトリルを用いて、実施例 147 と同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより、

15 表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.81–2.40 (7H, m), 3.56–3.88 (2H, m), 5.08–5.34 (1H, m), 6.75–7.70 (3H, m) 7.81–7.90 (1H, m), 8.33–8.63 (4H, m).

20 ESI-MS (m/e) : 426 [M+H]

実施例 159

25 5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリミジン-2-カルボキサミド

実施例 158 で得られた 5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリミジン-2-カルボニトリルを用いて、実施例 43 と同様の方法、

これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.79–2.42 (7H, m), 3.60–3.90 (2H, m), 5.18–5.39 (1H, m), 6.99–7.71 (3H, m), 7.82–7.92 (1H, m), 8.34–8.42 (1H, m), 8.55–8.65 (3H, m)
ESI-MS (m/e): 444 [M+H]

実施例 160

10 4-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)安息香酸 エチルエステル

4-フルオロ安息香酸 エチルエステルを用いて、実施例 147 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.24–1.41 (3H, m), 1.70–2.38 (7H, m), 3.53–3.87 (2H, m), 4.32–4.41 (2H, m), 5.14–5.45 (1H, m), 6.96–7.67 (5H, m), 7.82–7.91 (1H, m), 7.98–8.06 (2H, m), 8.34–8.43 (1H, m), 8.61–8.68 (1H, m)
20 ESI-MS (m/e): 471 [M+H]

実施例 161

1-(2-(6-フェネチルオキシ-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

25 (工程 1)

1-(2-(6-フェネチルオキシ-2-ピリジン-2-イル-3-(2-トリメチルシラニル-エトキシメチル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンの合成

実施例 121 (工程 10) で得られた 1-(2-(6-ヒドロキシ-2-ピ

リジン-2-イル-3-(2-トリメチルシラニル-エトキシメチル)-3
 H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン2
 9. 2mgのテトラヒドロフラン1ml溶液に、ジイソプロピルアミン0.0
 19ml、トリフェニルホスフィン27.6mg、2-フェニル-エタノール
 5 0.011mlを順次加え、反応液を室温で6時間攪拌した。反応液にジイソ
 プロピルアミン0.040ml、トリフェニルホスフィン53.2mg、2-
 フェニル-エタノール0.023mlを順次加え、反応液を室温で一終夜攪拌
 した。反応液に飽和重曹水を加え、酢酸エチルにて抽出、無水硫酸マグネシウ
 ムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラ
 10 フィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製) 酢酸
 エチル) にて精製し、表題化合物を褐色油状物質として得た。

(工程2)

1-(2-(6-フェネチルオキシ-2-ピリジン-2-イル-3H-ベン
 ズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンの製造
 15 1-(2-(6-フェネチルオキシ-2-ピリジン-2-イル-3-(2-
 トリメチルシラニル-エトキシメチル)-3H-ベンズイミダゾール-5-イ
 ル)-ピロリジン-1-イル)-エタノンを用いて、実施例121(工程1
 2)と同様な方法、これに準じた方法又はこれらと常法とを組み合わせること
 により、表題化合物を油状物質として得た。

20 ¹H NMR (CDCl₃) δ 1.59-2.23 (7H, m), 2.87-3.
 10, 3.50-3.86, 3.96-4.35 (6H, each m), 5.
 04-5.13, 5.46-5.57 (1H, each m), 6.53-7.
 55 (8H, m), 7.77-7.89 (1H, m), 8.32-8.40
 (1H, m), 8.54-8.65 (1H, m), 10.73-11.14
 25 (1H, m)

ESI-MS (m/e) : 427 [M+H]

実施例162

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン

(工程 1)

- 5 2 - (2 - フルオロ - 5 - ニトロ - フェニル) - ピロール - 1 - カルボン酸
t - ブチルエステルの合成

3 - ブロモ - 4 - フルオロ - ニトロベンゼン 4.3 g と 1 - (t - ブトキシカルボニル) ピロール - 2 - ボロン酸 5.0 g のジメトキシエタン 130 ml、及び水 22 ml の混合溶液に、テトラキストリフェニルホスフィンパラジウム

- 10 1.1 g、炭酸ナトリウム 4.2 g を加え、反応液を一終夜加熱還流した。反応液に飽和重曹水を加え、酢酸エチルで抽出し、有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝20／1）により精製し、表題化合物を黄色油状物として得た。

- 15 (工程 2)

2 - ((2 - (4 - メタンスルホニル - フェノキシ) - 5 - ニトロ - フェニル) - ピロール - 1 - カルボン酸 t - ブチルエステルの合成

2 - (2 - フルオロ - 5 - ニトロ - フェニル) - ピロール - 1 - カルボン酸
t - ブチルエステル 2.5 g と 4 - メタンスルホニル - フェノール 1.55 g

- 20 のジメチルホルムアミド 20 ml 溶液に、炭酸カリウム 3.38 g を加え、反応液を 100 度で 2 時間攪拌した。冷却後、反応液に水を加え、酢酸エチルで抽出し、有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した。

溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝2／1）により精製し、表題化合物を淡黄色

- 25 固体として得た。

(工程 3)

2 - (5 - アミノ - 2 - (4 - メタンスルホニル - フェノキシ) - フェニル) - ピロリジン - 1 - カルボン酸 t - ブチルエステルの合成

2 - ((2 - (4 - メタンスルホニル - フェノキシ) - 5 - ニトロ - フェニル) -

ル) - ピロール - 1 - カルボン酸 t - ブチルエステル 2. 87 g のエタノール溶液 120 ml に、5 % 白金炭素触媒 1. 0 g を加え、反応液を水素雰囲気下、一終夜攪拌した。触媒をセライトにて濾去し、溶媒を減圧留去した。得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル = 1 / 1 ~ 酢酸エチル) により精製し、表題化合物を白色固体として得た。

(工程 4)

1 - (2 - (5 - アミノ - 2 - (4 - メタンスルホニル - フェノキシ) - フェニル) - ピロリジン - 1 - イル) - 2, 2, 2 - トリフルオロ - エタノンの合成

2 - (5 - アミノ - 2 - (4 - メタンスルホニル - フェノキシ) - フェニル) - ピロリジン - 1 - カルボン酸 t - ブチルエステル 1. 51 g のベンゼン 25 ml 溶液に亜鉛粉末 342 mg とクロロギ酸ベンジル 650 mg を加え、反応液を室温で一終夜攪拌した。反応液をセライト濾過し、濾液に飽和重曹水を加え、酢酸エチルで抽出し、有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた粗生成物を 4 規定塩酸 - 1, 4 - ジオキサン溶液 20 ml に溶解し、反応液を室温で 3 時間攪拌した。反応液を減圧留去後、得られた粗生成物をクロロホルム 30 ml に溶解し、氷冷下ピリジン 2 ml と無水トリフルオロ酢酸 0. 5 ml を加え、反応液を室温で 2 時間攪拌した。反応液に 1 規定塩酸を加え、酢酸エチルで抽出し、有機層を水、飽和重曹水、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた粗生成物のメタノール 100 ml 溶液に 10 % パラジウム - 炭素触媒 50 mg を加え、反応液を水素雰囲気下、一終夜攪拌した。触媒をセライトにて濾去し、溶媒を減圧留去した。得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル = 1 / 1 ~ 1 / 3) により精製し、表題化合物を白色固体として得た。

(工程 5)

1 - (2 - (5 - アミノ - 2 - (4 - メタンスルホニル - フェノキシ) - 4 - ニトロ - フェニル) - ピロリジン - 1 - イル) - 2, 2, 2 - トリフルオ

ローエタノンの合成

- 1 - (2 - (5 - アミノ - 2 - (4 - メタンスルホニル - フェノキシ) - フェニル) - ピロリジン - 1 - イル) - 2, 2, 2 - トリフルオロ - エタノン 588 mg のトリフルオロ酢酸 2 ml 溶液に、硝酸カリウム 153 mg を加え、
5 反応液を室温で一終夜攪拌した。反応液に飽和重曹水を添加し中和した後、酢酸エチルで抽出し、有機層を飽和食塩水で洗浄、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／1）により精製し、表題化合物を黄色固体として得た。

10 (工程6)

2, 2, 2 - トリフルオロ - 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノンの合成

- 1 - (2 - (5 - アミノ - 2 - (4 - メタンスルホニル - フェノキシ) - 4 - ニトロ - フェニル) - ピロリジン - 1 - イル) - 2, 2, 2 - トリフルオ
15 ローエタノン 521 mg のエタノール 10 ml 溶液に、展開ラネーニッケル触媒 100 mg を加え、水素雰囲気下、反応液を一終夜攪拌した。触媒をセライトにて濾去し、溶媒を減圧留去し、粗生成物を得た。得られた粗生成物 448 mg のメタノール 10 ml 溶液に、ピリジン - 2 - カルボキサアルデヒド 22
20 6 mg を加え、反応液を 50 度で一終夜攪拌した。反応液に水を加え、酢酸エチルで抽出し、有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝20／1）により精製し、表題化合物を淡黄色固体として得た。

25 (工程7)

5 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - ピロリジン - 2 - イル - 1 H - ベンズイミダゾールの合成

2, 2, 2 - トリフルオロ - 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イ

ル) -ピロリジン-1-イル) -エタノン 375 mg のメタノール 16 ml、及び水 3 ml の混合溶液に、炭酸カリウム 500 mg を加え、反応液を室温で一終夜撹拌した。反応液を減圧留去し、飽和重曹水を加え希釈した後、酢酸エチルで抽出し、有機層を飽和食塩水で洗浄、無水硫酸ナトリウムで乾燥した。

- 5 溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム／メタノール／アンモニア水＝10／1／0.1）により精製し、表題化合物を淡黄色固体として得た。

（工程 8）

- 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノンの製造

- 5 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - ピロリジン - 2 - イル - 1 H - ベンズイミダゾール 10 mg の塩化メチレン 1 ml 溶液に、無水酢酸 0.003 ml を加えた後、反応液を室温で 1 時間
15 撹拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー（KieselgelTM 60 F₂₅₄, Art 5744（メルク社製）、クロロホルム／メタノール＝10／1）にて精製し、表題化合物を白色固体として得た。

- ¹H NMR (CDCl₃) δ : 1.60 - 2.40 (7H, m), 3.05 and
20 d 3.08 (total 3H, each s), 3.52 - 3.90 (2H, m), 5.13 - 5.37 (1H, m), 7.08 - 7.69 (5H, m), 7.83 - 7.97 (3H, m), 8.32 - 8.40 (1H, m), 8.61 - 8.70 (1H, m)

ESI-MS (m/e) : 477 [M+H]

- 25 実施例 163

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン エナンチオマー A 及び エナンチオマー B

実施例 162（工程 7）で得られた 5 - (4 - メタンスルホニル - フェノキ

シ) - 2 - ピリジン - 2 - イル - 6 - ピロリジン - 2 - イル - 1 H - ベンズイ
ミダゾール 230 mg を光学分割用カラム (CHIRALPAK AD 2 c
mφ × 25 cmL (ダイセル化学工業社製)、移動相: ヘキサン / 2 - プロパ
ノール / ジエチルアミン 20 / 80 / 0.1、流速: 10 ml / min) に
5 て光学分割し、エナンチオマー A (保持時間: 19.0 min)、エナンチオ
マー B (保持時間: 32.2 min) をそれぞれ黄色油状物質として得た。

実施例 164

10 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン -
2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - エタノン A

実施例 163 で得られた 1 - (2 - (6 - (4 - メタンスルホニル - フェノ
キシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) -
ピロリジン - 1 - イル) - エタノン エナンチオマー A 12 mg の塩化メチレ
ン 1 ml 溶液に、無水酢酸 0.003 ml を加えた後、反応液を室温で 1 時間
15 攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラ
フィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、ク
ロロホルム / メタノール = 10 / 1) にて精製し、表題化合物のキラル体の 1
つを白色固体として得た。

20 ¹H-NMR (CDCl₃) δ: 1.60 - 2.40 (7H, m), 3.05 a
nd 3.08 (total 3H, each s), 3.52 - 3.90 (2H,
m), 5.13 - 5.37 (1H, m), 7.08 - 7.69 (5H, m),
7.83 - 7.97 (3H, m), 8.35 - 8.43 (1H, m), 8.6
1 - 8.70 (1H, m)

25 ESI-MS (m/e): 477 [M+H]

比旋光度: [α]²⁴_D (c = 0.100, エタノール) -46.9 度

実施例 165

1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン -
2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - エタノン B

実施例 163 で得られた 1 - (2 - (6 - (4 - メタンスルホニル - フェノ
 5 キシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) -
 ピロリジン - 1 - イル) - エタノン エナンチオマー B 44 mg の塩化メチレ
 ン 1 ml 溶液に、無水酢酸 0.011 ml を加えた後、反応液を室温で 1 時間
 攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフ
 10 ィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロ
 ロホルム/メタノール = 10/1) にて精製し、表題化合物のキラル体の 1 つ
 を白色固体として得た。

ESI-MS (m/e) : 477 [M+H]

比旋光度: $[\alpha]^{24}_D$ (c = 0.100, エタノール) +47.7 度

15 実施例 166

2, 2, 2 - トリフルオロ - 1 - (2 - (6 - (4 - フルオロ - フェノキ
シ) - 2 - ピリジン - 2 - イル - 3 H - ベンゾイミダゾール - 5 - イル) - ピ
ロリジン - 1 - イル) - エタノン

4 - フルオロフェノールを用いて、実施例 162 (工程 2) ~ (工程 6) と
 20 同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
 表題化合物を白色固体として得た。

¹H NMR (CDCl₃) δ : 1.96 - 2.21 (3H, m), 2.31 - 2.
 43 (1H, m), 3.77 - 4.08 (2H, m), 5.47 - 5.70
 (1H, m), 6.88 - 6.91 (1H, m), 7.00 - 7.08 (4H,
 25 m), 7.26 - 7.50 (2H, m), 7.82 - 7.85 (1H, m),
 8.31 - 8.35 (1H, m), 8.57 - 8.61 (1H, m)

ESI-MS (m/e) : 471 [M+H]

実施例 167

1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンゾイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

4-フルオロフェノールを用いて、実施例162(工程2)～(工程8)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
5 表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.83–2.03 (6H, m), 2.32–2.41 (1H, m), 3.58–3.86 (2H, m), 5.26–5.57 (1H, m), 6.96–7.06 (5H, m), 7.24–7.35 (2H, m), 7.80–7.88 (1H, m), 8.30–8.37 (1H, m),
10 8.56–8.62 (1H, m)

ESI-MS (m/e): 417 [M+H]

実施例168

1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンゾイミダゾール-5-イル)-ピロリジン-1-イル)-2-ヒドロキシ-エタノン

4-フルオロフェノールを用いて、実施例162(工程2)～(工程7)と同様な方法で得られた5-(4-フルオロフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンゾイミダゾール20mgのクロロホルム1ml溶液に、グリコール酸4.5mg、N-ヒドロキシベンゾトリアゾール水和物12.3mg及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド塩酸塩15.4mgを順次加え、反応液を室温で一昼夜攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー(KieselgelTM 60F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1)にて精製し、表題化合物を得た。
25

$^1\text{H NMR}$ (CDCl_3) δ : 1.88–2.13 (3H, m), 2.20–2.43 (1H, m), 3.40–4.21 (4H, m), 5.14–5.60 (1H, m), 6.85–7.54 (7H, m), 7.78–7.86 (1H, m), 8.29–8.37 (1H, m), 8.56–8.61 (1H, m)

ESI-MS (m/e) : 433 [M+H]

実施例169

1- (2- (6- (4-フルオロフェノキシ) -2-ピリジン-2-イル-
5 3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -2-メト
キシエタノン

メトキシ酢酸を用いて、実施例168と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

¹HNMR (CDCl₃) δ : 1.80-2.41 (4H, m), 3.26-3.
10 46 (3H, m), 3.52-4.16 (4H, m), 5.28-5.60
(1H, m), 6.79-7.57 (7H, m), 7.77-7.85 (1H,
m), 8.28-8.38 (1H, m), 8.56-8.62 (1H, m)

ESI-MS (m/e) : 447 [M+H]

15 実施例170

1- (2- (6- (4-フルオロフェノキシ) -2-ピリジン-2-イル-
3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -3-フェ
ニルプロパン-1-オン

3-フェニルプロピオン酸を用いて、実施例168と同様の方法、これに
20 準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

¹HNMR (CDCl₃) δ : 1.82-3.03 (8H, m), 3.48-3.
93 (2H, m), 5.13-5.99 (1H, m), 6.82-7.60
(12H, m), 7.80-7.08 (1H, m), 8.09-8.39 (1
25 H, m), 8.56-8.66 (1H, m)

ESI-MS (m/e) : 507 [M+H]

実施例171

(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3
H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-(2R)-
ピロリジン-2-イル-メタノン

実施例168で得られた5-(4-フルオロフェノキシ)-2-ピリジ
ン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール20m
gのクロロホルム1ml溶液に、1-t-ブトキシカルボニル-D-プロリン
13.8mg、N-ヒドロキシベンゾトリアゾール水和物12.3mg及び
1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド塩酸塩15.
4mgを順次加え、反応液を室温で一終夜攪拌した。反応溶媒を減圧留去後、
得られた残渣を4規定塩酸-酢酸エチル溶液1mlに溶解し、反応液を室温に
て1時間攪拌した。溶媒を減圧留去し、得られた残渣を薄層クロマトグラ
フィー(NH TLCプレート(FUJISILYSIA CHEMICAL社製)、クロロホルム/メタノール=30/1)にて精製し、表題化合物を
油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 0.82-4.00 (13H, m), 5.23-
5.61 (1H, m), 6.82-7.59 (7H, m), 7.78-7.8
8 (1H, m), 8.32-8.39 (1H, m), 8.57-8.64 (1
H, m)

ESI-MS (m/e): 472 [M+H]

20

実施例172

(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3
H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-(2S)-
ピロリジン-2-イル-メタノン

1-t-ブトキシカルボニル-L-プロリンを用いて、実施例171と同様
の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表
題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 0.82-4.00 (13H, m), 5.23-
5.61 (1H, m), 6.82-7.59 (7H, m), 7.78-7.8

8 (1H, m), 8.30-8.39 (1H, m), 8.57-8.64 (1H, m)

ESI-MS (m/e) : 472 [M+H]

5 実施例173

2-ジメチルアミノ-1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

10 N, N-ジメチルグリシン塩酸塩を用いて、実施例168と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、油状物質として得た。

¹HNMR (CDCl₃) δ : 1.81-2.57 (10H, m), 2.76-3.96 (4H, m), 5.41-5.62 (1H, m), 6.94-7.37 (7H, m), 7.81-7.89 (1H, m), 8.33-8.38 (1H, m), 8.59-8.68 (1H, m)

ESI-MS (m/e) : 460 [M+H]

実施例174

20 1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-プロパン-1-オン

プロピオン酸を用いて、実施例168と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

25 ¹HNMR (CDCl₃) δ : 0.95-1.24 (3H, m), 1.70-2.60 (6H, m), 3.52-3.94 (2H, m), 5.24-5.62 (1H, m), 6.75-7.66 (7H, m), 7.77-7.92 (1H, m), 8.27-8.44 (1H, m), 8.52-8.68 (1H, m), 10.66-11.08 (1H, m)

ESI-MS (m/e) : 431 [M+H]

実施例 175

1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-
3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-ブタン-
5 1-オン

n-酪酸を用いて、実施例 168 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 0.70-1.07 (3H, m), 1.40-2.44 (8H, m), 3.53-3.91 (2H, m), 5.25-5.60
10 (1H, m), 6.72-7.66 (7H, m), 7.80-7.93 (1H, m), 8.30-8.44 (1H, m), 8.53-8.68 (1H, m), 10.68-11.18 (1H, m)

ESI-MS (m/e): 445 [M+H]

15 実施例 176

1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-
3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-3-ヒド
ロキシプロパン-1-オン

3-ヒドロキシプロピオン酸を用いて、実施例 168 と同様の方法、これに
20 準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.43-2.73 (6H, m), 3.24-4.27 (5H, m), 5.24-5.60 (1H, m), 6.75-7.60 (7H, m), 7.76-7.88 (1H, m), 8.27-8.40 (1H,
25 m), 8.53-8.66 (1H, m), 10.44-11.01 (1H, m)

ESI-MS (m/e): 447 [M+H]

実施例 177

1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-2-メチルアミノエタノン

N-tert-ブトキシカルボニル-N-メチルグリシンを用いて、実施例171
5 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.82-2.01 (3H, m), 2.43-2.56 (4H, m), 3.25-4.15 (4H, m), 5.32-5.37 (1H, m), 7.00-7.31 (4H, m), 7.38-7.58 (2H, m), 8.03-8.08 (1H, m), 8.37-8.43 (1H, m), 8.69-8.79 (1H, m), 8.80-8.94 (1H, m),
10

ESI-MS (m/e): 446 [M+H]

実施例178

15 5-(4-フルオロフェノキシ)-6-(1-メタンスルホニル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例168で得られた5-(4-フルオロフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール20mg
の酢酸エチル1ml溶液に、トリエチルアミン0.01ml及び塩化メタンスルホニル0.005mlを順次加え、反応液を室温で一終夜攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー(KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1)にて精製し、表題化合物を白色固体として得た。
20

$^1\text{H NMR}$ (CDCl_3) δ : 1.80-2.08 (3H, m), 2.28-2.42 (1H, m), 2.81 and 2.84 (total 3H, each s), 3.47-3.74 (2H, m), 5.17-5.37 (1H, m), 6.79-7.93 (8H, m), 8.30-8.37 (1H, m), 8.57-8.61 (1H, m)
25

ESI-MS (m/e): 453 [M+H]

実施例 179

5-(4-フルオロフェノキシ)-2-ピリジン-2-イル-6-(1-ピロリジン-2-イル-ピロリジン-2-イル)-1H-ベンズイミダゾール

- 5 実施例 168 で得られた 5-(4-フルオロフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール 17.1 mg のエタノール 2 ml 溶液に、トリエチルアミン 0.013 ml 及び 2-クロロピリミジン 6.3 mg を順次加え、反応液を 3 時間加熱還流した。反応溶媒を減圧留去後、得られた残渣を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションを酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を白色個体として得た。
- 10 S-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションを酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を白色個体として得た。

- $^1\text{H NMR}$ (CDCl_3) δ : 1.98-2.15 (3H, m), 2.34-2.42 (1H, m), 3.68-3.78 (1H, m), 3.90-4.07 (1H, m), 5.63 (1H, d, $J=8.0\text{ Hz}$), 6.43 (1H, br s), 6.87-7.55 (7H, m), 7.79-7.84 (1H, m), 8.15-8.34 (3H, m), 8.55-8.58 (1H, m)
- ESI-MS (m/e): 453 [$M+H$]
- 20

実施例 180

2-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-アセトアミド

- 25 実施例 168 で得られた 5-(4-フルオロフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール 20 mg のアセトニトリル 1 ml 溶液に、炭酸カリウム 11.4 mg、及びヨードアセトアミド 11.1 mg を順次加え、反応液を室温にて一終夜攪拌した。反応液を濃縮後、得られた残渣を逆相中圧液体クロマトグラフィー (ODS-AS-

360-CC (YMC社製) 移動相: 水-アセトニトリル-0.1%トリフル
 オロ酢酸) にて精製し、得られたフラクションを酢酸エチルにて希釈し、飽和
 重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を
 減圧留去し、表題化合物を白色固体として得た。

5 $^1\text{H NMR}$ (CDCl_3) δ : 1.60-2.04 (3H, m), 2.20-2.
 13 (1H, m), 2.80-2.85 (1H, m), 3.37-3.44
 (2H, m), 3.96-4.03 (1H, m), 5.41-5.52 (1H,
 m), 6.90-7.34 (5H, m), 7.36-7.39 (1H, m),
 7.65 and 8.00 (total 1H, each s), 7.83-7.8
 10 7 (1H, m), 8.36-8.39 (1H, m), 8.59-8.64 (1
 H, m)

ESI-MS (m/e): 432 $[\text{M}+\text{H}]$

実施例181

15 2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-
 ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸 エチルエス
 テル

実施例168で得られた5-(4-フルオロフェノキシ)-2-ピリジン
 -2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール20mg
 20 のベンゼン1ml溶液に、亜鉛粉末5.2mg及びクロロギ酸エチル0.00
 6mlを順次加え、反応液を室温で一終夜攪拌した。反応溶媒を減圧留去し、
 得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1)
 にて精製し、表題化合物を白色固体として得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 1.23-1.31 (3H, m), 1.80-2.
 00 (3H, m), 2.20-2.39 (1H, m), 3.50-3.79
 (2H, m), 3.91-4.17 (2H, m), 5.17-5.38 (1H,
 m), 6.81-7.63 (7H, m), 7.77-7.85 (1H, m),
 8.28-8.39 (1H, m), 8.55-8.63 (1H, m)

ESI-MS (m/e) : 447 [M+H]

実施例182

5 2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド

実施例162(工程7)で得られた5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール17.1mgの塩化メチレン1ml溶液に、ジメチルアミノピリジン5mg及びイソシアン酸トリメチルシリル0.029mlを順次加え、反応液を室温で一終夜攪拌した。反応液に水を加え、酢酸エチルで抽出した後、飽和食塩水で洗浄した。乾燥及び濃縮後、得られた残渣を逆相中圧液体クロマトグラフィー(ODS-AS-360-CC(YMC社製)移動相:水-アセトニトリル-0.1%トリフルオロ酢酸)にて精製し、得られたフラクションを
15 酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を白色固体として得た。

¹H NMR (CDCl₃) δ: 1.83-2.09 (3H, m), 2.22-2.40 (1H, m), 3.07 (3H, s), 3.56-3.82 (2H, m), 4.35 and 4.62 (total 2H, each brs), 5.01-5.20 (1H, m), 7.08-7.95 (8H, m), 8.34-8.40 (1H, m), 8.62-8.64 (1H, m)

ESI-MS (m/e) : 478 [M+H]

実施例183-1、183-2

25 2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド エナンチオマーA及びエナンチオマーB

実施例182で得られたラセミ体の2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル

ル) -ピロリジン-1-カルボキサミド 10 mg を光学分割用カラム (CHIRALPAK AD 2 cmφ×25 cmL (ダイセル化学工業社製)、移動相: ヘキサン/エタノール 20/80、流速: 10 ml/min) にて光学分割し、エナンチオマーA (保持時間: 17.9 min)、エナンチオマーB (保持時間: 27.6 min) をそれぞれ白色固体として得た。

エナンチオマーA

ESI-MS (m/e): 478 [M+H]

比旋光度: $[\alpha]^{24}_D$ (c=0.100, エタノール) -27.4度

エナンチオマーB

10 ESI-MS (m/e): 478 [M+H]

比旋光度: $[\alpha]^{24}_D$ (c=0.100, エタノール) +28.4度

実施例184

15 2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド

実施例168で得られた5-(4-フルオロフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール 31.2 mg の塩化メチレン 1 ml 溶液に、ジメチルアミノピリジン 2 mg、及びイソシアン酸トリメチルシリル 0.059 ml を順次加え、反応液を室温で一終夜
20 攪拌した。反応液に水を加え、酢酸エチルで抽出した後、飽和食塩水で洗浄した。乾燥及び濃縮後、得られた残渣を逆相中圧液体クロマトグラフィー (ODS-AS-360-CC (YMC社製) 移動相: 水-アセトニトリル-0.1%トリフルオロ酢酸) にて精製し、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl₃) δ : 1.88-2.08 (3H, m), 2.32-2.48 (1H, m), 3.62-3.87 (2H, m), 4.34 and 4.71 (total 2H, each brs), 5.15-5.30 (1H, m), 6.91-7.73 (7H, m), 7.81-7.87 (1H, m), 8.31-8.37 (1H, m), 8.59-8.61 (1H, m)

ESI-MS (m/e): 418 [M+H]

実施例 185-1、185-2

2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド エナン

5 チオマーA及びエナンチオマーB

実施例 184 で得られたラセミ体の 2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド 9.0 mg を光学分割用カラム (CHIRAL PAK AD 2 cmφ×25 cmL (ダイセル化学工業社製)、移動相: ヘキサン/2-プロパノール 50/50、流速: 10 ml/min) にて光学分割し、エナンチオマーA (保持時間: 12.1 min)、エナンチオマーB (保持時間: 26.9 min) をそれぞれ白色固体として得た。

エナンチオマーA

E SI-MS (m/e) : 418 [M+H]

15 エナンチオマーB

E SI-MS (m/e) : 418 [M+H]

実施例 186

20 2-(6-(4-ジメチルカルバモイルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド

4-ヒドロキシ-N,N-ジメチルベンズアミドを用いて、実施例 162 (工程 2) ~ (工程 7)、及び実施例 182 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として
25 得た。

¹H NMR (CDCl₃) δ : 1.85-2.07 (3H, m), 2.28-2.43 (1H, m), 3.00-3.18 (6H, m), 3.60-3.80 (2H, m), 5.10-5.23 (1H, m), 7.01-7.76 (7H,

m), 7.83-7.88 (1H, m), 8.33-8.39 (1H, m),
8.63-8.64 (1H, m)

ESI-MS (m/e) : 471 [M+H]

5 実施例187-1、187-2

2-(6-(4-ジメチルカルバモイルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド エナンチオマーA及びエナンチオマーB

実施例186で得られたラセミ体の2-(6-(4-ジメチルカルバモイルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボキサミド72.2mgを光学分割用カラム(CHIRALPAK AD 2cmφ×25cmL(ダイセル化学工業社製)、移動相:ヘキサン/エタノール 40/60、流速:10ml/min)にて光学分割し、エナンチオマーA(保持時間:18.1min)、エナンチオマーB(保持時間:23.9min)をそれぞれ白色固体として得た。

エナンチオマーA

ESI-MS (m/e) : 471 [M+H]

エナンチオマーB

ESI-MS (m/e) : 471 [M+H]

20

実施例188

2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸エチルアミド

イソシアン酸エチルを用いて、実施例184と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H-NMR (CDCl₃) δ : 0.94-1.07 (3H, m), 1.80-2.03 (3H, m), 2.25-2.41 (1H, m), 3.10-3.26 (2H, m), 3.57-3.74 (2H, m), 4.02-4.14 (1

H, m), 5.07–5.23 (1H, m), 6.85–7.66 (7H, m), 7.78–7.85 (1H, m), 8.30–8.38 (1H, m), 8.54–8.63 (1H, m)

ESI-MS (m/e) : 446 [M+H]

5

実施例189

1-(2-(6-(4-フルオロフェノキシ)-2-ピラジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

ピラジン-2-カルボキサアルデヒドを用いて、実施例162 (工程6) ~ (工程8) と同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより表題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1.86–2.08 (7H, m), 3.37–3.90 (2H, m), 5.27–5.55 (1H, m), 6.76–7.64 (6H, m), 8.32–8.62 (2H, m), 9.53–9.56 (1H, m)

15

ESI-MS (m/e) : 418 [M+H]

実施例190

1-(2-(6-(4-フルオロフェノキシ)-2-チアゾール-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

チアゾール-2-カルボキサアルデヒドを用いて、実施例162 (工程6) ~ (工程8) と同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

¹HNMR (CDCl₃) δ : 1.60–2.23 (6H, m), 2.24–2.43 (1H, m), 3.50–3.88 (2H, m), 5.28–5.57 (1H, m), 6.64–7.62 (7H, m), 7.89–7.94 (1H, m)

25

ESI-MS (m/e) : 423 [M+H]

実施例 191

(1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-メタ
 5 ノール

D, L-プロリノールを用いて、実施例 15 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.64–1.92 (3H, m), 1.97–2.06 (1H, m), 3.00–3.12 (1H, m), 3.04 (3H, s),
 10 3.38–3.46 (1H, m), 3.53–3.64 (2H, m), 3.84 (1H, brs), 6.98 (2H, d, $J=8.6\text{ Hz}$), 7.10 and 7.22 (total 1H, each s), 7.33–7.40 (1H, m), 7.50–7.57 (1H, m), 7.80–7.90 (3H, m) 8.34–8.41 (1H, m), 8.62–8.63 (1H, m)
 15 ESI-MS (m/e): 465 [M+H]

実施例 192

1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-カルボン酸
 20 メチルエステル

D, L-プロリン メチルエステル塩酸塩を用いて、実施例 15 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.83–2.03 (3H, m), 2.20–2.28 (1H, m), 3.05 (3H, s), 3.20–3.86 (2H, m),
 25 3.54 (3H, s), 4.28–4.53 (1H, m), 6.91–7.37 (3H, m), 7.32–7.38 (2H, m) 7.81–7.87 (3H, m), 8.30–8.39 (1H, m), 8.61–8.62 (1H, m)
 ESI-MS (m/e): 493 [M+H]

実施例 193

1- (6- (4-メタンスルホニル-フェノキシ) -2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) -ピロリジン-2-カルボン酸
5 メチルアミド

DL-プロリン メチルアミド塩酸塩を用いて、実施例 15 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80-2.03 (3H, m), 2.25-2.40 (1H, m), 2.46-2.53 (3H, m), 3.06 (3H, s),
10 3.20-3.26 (1H, m), 3.60-3.78 (1H, m), 4.18-4.24 (1H, m), 7.02-7.60 (3H, m), 7.03 (2H, d, $J=9.0\text{ Hz}$), 7.82-7.92 (1H, m), 7.89 (2H, d, $J=9.0\text{ Hz}$), 8.35 (1H, d, $J=7.4\text{ Hz}$), 8.6
15 3 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 492 [$M+H$]

実施例 194

1- (6- (4-メタンスルホニル-フェノキシ) -2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) -ピロリジン-2-カルボキサミド
20 ド

DL-プロリン アミド塩酸塩を用いて、実施例 15 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.91-2.03 (3H, m), 2.26-2.50 (1H, m), 3.02 and 3.06 (total 3H, each s),
25 3.18-3.28 (1H, m), 3.63-3.91 (1H, m), 4.13-4.29 (1H, m), 6.04-6.33 (1H, m), 6.86-7.28 (4H, m), 7.37-7.41 (1H, m), 7.48-7.54

(1H, m), 7.80–7.92 (3H, m), 8.34–8.38 (1H, m), 8.48–8.63 (1H, m)

ESI-MS (m/e) : 478 [M+H]

5 実施例 195

1-(2-(6-(4-フルオロフェノキシ)-2-ピリジン-2-イル-3H-ベンゾイミダゾール-5-イル)-ピペリジン-1-イル)-エタノン

(工程 1)

2-(2-フルオロ-5-ニトロフェニル)-ピリジンの合成

- 10 3-ブロモ-4-フルオロニトロベンゼン 2.1 g と 2-トリメチルスズ-ピリジン 2.3 g の 1, 4-ジオキサン 20 ml 溶液にテトラキストリフェニルホスフィンパラジウム 0.55 g を加え、反応液を一終夜加熱還流した。反応液に飽和重曹水を加え、酢酸エチルで抽出し、有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル = 7/1）により精製し、表題化合物を黄色固体として得た。

(工程 2)

2-(2-(4-フルオロフェノキシ)-5-ニトロフェニル)-ピリジンの合成

- 20 4-フルオロ-3-ピリジルニトロベンゼン 6.00 mg と 4-フルオロフェノール 3.47 mg のジメチルホルムアミド 10 ml 溶液に、炭酸カリウム 7.13 mg を加え、反応液を 100 度で 1 時間攪拌した。冷却後、反応液に水を加え、酢酸エチルで抽出し、有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル = 5/1）により精製し、表題化合物を淡黄色固体として得た。

(工程 3)

(4-(4-フルオロフェノキシ)-3-ピリジン-2-イルフェニル)-カルバミン酸 t-ブチルエステルの合成

2 - (2 - (4 - フルオロフェノキシ) - 5 - ニトロフェニル) - ピリジン 840 mg の酢酸エチル 10 ml 溶液に 10 % パラジウム - 炭素触媒 100 mg を加え、反応液を水素雰囲気下、一終夜撹拌した。触媒をセライトにて
5 濾去し、溶媒を減圧留去し、粗生成物を得た。得られた粗生成物のテトラヒドロフラン 10 ml 溶液に、二炭酸ジ-tert-ブチル 1.5 g を加え、反応液を 60 度で一終夜撹拌した。反応液を冷却後、溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル = 10 / 1）により精製し、表題化合物を白色固体として得た。

10 (工程 4)

1 - (2 - (5 - アミノ - 2 - (4 - フルオロフェノキシ) - フェニル) - ピペリジン - 1 - イル) - エタノンの合成

(4 - (4 - フルオロフェノキシ) - 3 - ピリジン - 2 - イル - フェニル) - カルバミン酸 tert-ブチルエステル 300 mg のエタノール 20 ml 溶液
15 に、無水酢酸 0.3 ml と 10 % パラジウム - 炭素触媒 100 mg を加え、反応液を水素雰囲気下、一終夜撹拌した。触媒をセライトにて濾去し、濾液を減圧留去し、粗生成物を得た。得られた粗生成物を 4 規定塩酸 - 1, 4 - ジオキサン溶液 5 ml に溶解し、反応液を室温で 1 時間撹拌した。反応液に飽和重曹水を添加し、酢酸エチルで抽出し、有機層を飽和食塩水で洗浄し、無水硫酸ナ
20 トリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル = 1 / 1 ~ 酢酸エチル）により精製し、表題化合物を淡黄色固体として得た。

(工程 5)

1 - (2 - (5 - アミノ - 2 - (4 - フルオロフェノキシ) - 4 - ニ
25 ローフェニル) - ピペリジン - 1 - イル) - エタノンの合成

1 - (2 - (5 - アミノ - 2 - (4 - フルオロフェノキシ) - フェニル) - ピペリジン - 1 - イル) - エタノン 190 mg のトリフルオロ酢酸 1 ml 溶液に、硝酸カリウム 64 mg を加え、反応液を室温で一終夜撹拌した。反応液に飽和重曹水を添加し中和した後、酢酸エチルで抽出し、有機層を飽和食

塩水で洗浄、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去した後、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／1）により精製し、表題化合物を黄色固体として得た。

（工程6）

- 5 1-（2-（6-（4-フルオロフェノキシ）-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル）-ピペリジン-1-イル）-エタノンの製造

- 1-（2-（5-アミノ-2-（4-フルオロフェノキシ）-4-ニトロフェニル）-ピペリジン-1-イル）-エタノン180mgのエタノール
 10 10ml溶液に、展開ラネーニッケル触媒50mgを加え、反応液を水素雰囲気下、一終夜撹拌した。触媒をセライトにて濾去し、濾液を減圧留去し、粗生成物を171mg得た。得られた粗生成物50mgをN-メチルピロリドン1mlに溶解し、ピリジン-2-カルボキサアルデヒド16mgを加え、反応液を室温で3日間撹拌した。反応液に水を加え、酢酸エチルで抽出し、有機層を
 15 水、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、反応混合物を逆相中圧液体クロマトグラフィー（ODS-AS-360-CC（YMC社製）移動相：水-アセトニトリル-0.1%トリフルオロ酢酸）により精製し、表題化合物を淡黄色固体として得た。

- ¹H NMR (CDCl₃) δ: 1.60-1.85 (3H, m), 1.92-2.09 (5H, m), 2.22-2.30 (1H, m), 3.50-3.78 (2H, m), 5.35-5.38 (1H, m), 6.94-7.08 (5H, m), 7.32-7.38 (2H, m), 7.84-7.89 (1H, m), 8.35-8.38 (1H, m), 8.62-8.67 (1H, m)
 20 ESI-MS (m/e): 431 [M+H]

25

実施例196

5-（2-シアノフェノキシ）-2-ピリジン-2-イル-6-（6-メタ
 ンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール

（工程1）

(3-フルオロ-4-ヒドロキシフェニル)-カルバミン酸 tert-ブチルエステルの合成

3-フルオロ-4-ヒドロキシニトロベンゼン 6.15 g、及び二炭酸ジ-tert-ブチル 930 mg のメタノール 100 ml 溶液に、10%パラジウム-炭素触媒 600 mg を加え、反応液を水素雰囲気下、一終夜撹拌した。触媒を濾去後、溶媒を減圧留去し、残渣を酢酸エチル-ヘキサン混合溶媒で濾取することにより、表題化合物を得た。

(工程2)

(3-フルオロ-4-(6-メタンスルホニルピリジン-3-イルオキシ)-フェニル)-カルバミン酸 tert-ブチルエステルの合成

(工程1)で得られた(3-フルオロ-4-ヒドロキシフェニル)-カルバミン酸 tert-ブチルエステル 4.74 g のN-メチルピロリジノン 50 ml 溶液に、5-クロロ-2-メタンスルホニルピリジン 4.00 g、及び炭酸セシウム 8.80 g を加え、反応液を 100 度にて 2 時間撹拌した。反応液を、酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=1/1)にて精製し、表題化合物を得た。

(工程3)

5-フルオロ-4-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ニトロフェニルアミンの合成

(工程2)で得られた(3-フルオロ-4-(6-メタンスルホニルピリジン-3-イルオキシ)-フェニル)-カルバミン酸 tert-ブチルエステル 3.38 g のトリフルオロ酢酸 35 ml 溶液に、硝酸カリウム 0.98 g を加え、反応液を室温にて 1 時間撹拌した後、溶媒を減圧留去した。残渣を酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=1/2)にて精製し、表題化合物を得た。

(工程4)

5 - (2-シアノフェノキシ) - 4 - (6-メタンスルホニルピリジン-3-イルオキシ) - 2-ニトロフェニルアミンの合成

(工程3)で得られた5-フルオロ-4-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ニトロフェニルアミン150mgのN-メチルピロリジノン2ml溶液に、2-ヒドロキシベンゾニトリル60mg、及び炭酸カリウム70mgを加え、反応液を90度にて5時間攪拌した。反応液に水を加えた後、沈殿物を濾取することにより、表題化合物を得た。

(工程5)

10 4 - (2-シアノフェノキシ) - 5 - (6-メタンスルホニルピリジン-3-イルオキシ) - ベンゼン-1, 2-ジアミンの合成

(工程4)で得られた5-(2-シアノフェノキシ)-4-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ニトロフェニルアミン161mgのメタノール5ml溶液に、展開ラネーニッケル触媒20mgを加え、
15 反応液を水素雰囲気下、一終夜攪拌した。触媒を濾去後、溶媒を減圧留去し、表題化合物を得た。

(工程6)

5 - (2-シアノフェノキシ) - 2-ピリジン-2-イル-6 - (6-メタンスルホニルピリジン-3-イルオキシ) - 1H-ベンズイミダゾールの
20 製造

(工程5)で得られた4-(2-シアノフェノキシ)-5-(6-メタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン37mgのメタノール1ml溶液に、ピリジン-2-カルボキサアルデヒド0.007ml及びニトロベンゼン0.5mlを加え、反応液を120度にて一終夜攪拌した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:クロロホルム/メタノール=20/1)、及び分取用薄層クロマトグラフィー(Kieselgel TM60F254, Art 5744 (メルク社製)、クロロホルム/メタノール=15/1)にて精製し、表題化合物を褐色固体として得た。

^1H NMR (CD_3OD) δ : 3.20 (3H, s), 6.94 (1H, d, $J=7.8\text{ Hz}$), 7.22 (1H, t, $J=7.8\text{ Hz}$), 7.41–7.47 (1H, m), 7.47 (1H, t, $J=7.8\text{ Hz}$), 7.53 (1H, dd, $J=7.8, 2.3\text{ Hz}$), 7.56–7.61 (1H, m), 7.66 (1H, d, $J=7.8\text{ Hz}$), 7.72 (1H, s), 7.78 (1H, s), 8.04 (1H, d, $J=7.8\text{ Hz}$), 8.26 (1H, d, $J=2.3\text{ Hz}$), 8.35 (1H, d, $J=7.8\text{ Hz}$), 8.80 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 484 $[\text{M}+\text{H}]$

10

実施例 197

5-(2-シアノフェノキシ)-2-ピラジン-2-イル-6-(6-メタ
ンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 196 (工程 5) で得られた 4-(2-シアノフェノキシ)-5-(6-メタ
15 (6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-
ジアミン 72 mg のジメチルホルムアミド 2 ml 溶液に、ピラジン-2-カル
ボン酸 21 mg、ヒドロキシベンゾトリアゾール 52 mg、及び 1-(3-ジ
メチルアミノプロピル)-3-エチルカルボジイミド・一塩酸塩 52 mg を加
え、反応液を室温にて 1 時間攪拌した。反応液を、酢酸エチルにて希釈し、飽
20 和重曹水、水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。
溶媒を減圧留去し、得られた残渣を N-メチルピロリジノン 1 ml に溶解し、
三トリフルオロメタンスルホン酸イッテルビウム 20 mg を加え、反応液を 1
60 度にて 2 時間攪拌した。反応液を、酢酸エチルにて希釈し、飽和重曹水、
飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去
25 し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: クロロ
ホルム/メタノール=30/1)、及び分取用薄層クロマトグラフィー (K i
e s e l g e l T M 6 0 F 2 5 4、A r t 5 7 4 4 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を褐色固体として得た。

^1H NMR (CD_3OD) δ : 3.20 (3H, s), 6.93 (1H, d, $J=7.6\text{ Hz}$), 7.21 (1H, t, $J=7.6\text{ Hz}$), 7.43 (1H, dd, $J=8.6, 2.3\text{ Hz}$), 7.58 (1H, t, $J=7.6\text{ Hz}$), 7.66 (1H, d, $J=7.6\text{ Hz}$), 7.67–7.90 (2H, m), 8.03 (1H, d, $J=8.6\text{ Hz}$), 8.25 (1H, d, $J=2.3\text{ Hz}$), 8.74 (1H, d, $J=2.3\text{ Hz}$), 8.81 (1H, d, $J=2.3\text{ Hz}$), 9.53 (1H, s)

ESI-MS (m/e): 485 [$\text{M}+\text{H}$]

10 実施例198

5-(2-カルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例196で得られた5-(2-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例43と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CD_3OD) δ : 3.23 (3H, s), 6.85–6.91 (1H, m), 7.17 (1H, t, $J=7.8\text{ Hz}$), 7.40–7.45 (2H, m), 7.53 (1H, dd, $J=7.8, 4.3\text{ Hz}$), 7.55–7.78 (1H, m), 7.88 (1H, dd, $J=7.8, 2.3\text{ Hz}$), 7.99 (1H, d, $J=8.6\text{ Hz}$), 8.02 (1H, td, $J=7.8, 2.3\text{ Hz}$), 8.27 (1H, d, $J=2.3\text{ Hz}$), 8.34 (1H, d, $J=7.8\text{ Hz}$), 8.78 (1H, d, $J=4.3\text{ Hz}$)

ESI-MS (m/e): 502 [$\text{M}+\text{H}$]

実施例199

5 - (2 - カルバモイル - フェノキシ) - 2 - ピラジン - 2 - イル - 6 -
(6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベンズイミダ
ゾール

実施例 197 で得られた 5 - (2 - シアノ - フェノキシ) - 2 - ピラジン -
5 2 - イル - 6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 1
H - ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方
法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体とし
て得た。

¹H NMR (CD₃OD) δ : 3.22 (3H, s), 6.87 - 6.91 (1
10 H, m), 7.15 - 7.22 (1H, m), 7.41 - 7.46 (2H,
m), 7.51 - 7.85 (2H, m), 7.87 (1H, dd, J = 7.8,
2.3 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.25 - 8.28
(1H, m), 8.73 - 8.75 (1H, m), 8.80 - 8.82 (1H,
m), 9.51 - 9.54 (1H, m)
15 ESI-MS (m/e) : 503 [M+H]

実施例 200

5 - (2 - フルオロ - フェノキシ) - 2 - ピリジン - 2 - イル - 6 - (6 - メ
タンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベンズイミダゾール

20 実施例 196 (工程 3) で得られた 5 - フルオロ - 4 - (6 - メタンスルホ
ニル - ピリジン - 3 - イルオキシ) - 2 - ニトロ - フェニルアミン、及び 2 -
フルオロフェノールを用いて、実施例 196 (工程 4) ~ (工程 6) と同様の
方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
化合物を無色固体として得た。

25 ¹H NMR (CDCl₃) δ : 3.20 (3H, s), 6.97 - 7.04 (1
H, m), 7.05 - 7.15 (3H, m), 7.33 (1/2H, dd, J
= 8.8, 2.8 Hz), 7.34 (1/2H, dd, J = 8.8, 2.8 H
z), 7.36 - 7.42 (1H, m), 7.42 (1/2H, s), 7.7
0 (1/2H, s), 7.86 - 7.91 (1H, m), 7.99 (1/2H,

d, $J=8.8\text{ Hz}$), 8.00 (1/2H, d, $J=8.8\text{ Hz}$), 8.34-8.40 (1H, m), 8.44 (1H, d, $J=2.8\text{ Hz}$), 8.61-8.65 (1H, m), 10.85 (1/2H, brs), 10.96 (1/2H, brs)

5 ESI-MS (m/e): 477 [M+H]

実施例201

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-メ
タンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

10 実施例200で得られた4-(2-フルオロフェノキシ)-5-(6-メ
タンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、
及びピラジン-2-カルボン酸を用いて、実施例197と同様の方法、これに
準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色
固体として得た。

15 $^1\text{H NMR}$ (CDCl_3) δ : 3.21 (3H, s), 7.02-7.08 (1
H, m), 7.09-7.17 (3H, m), 7.11 (1/2H, s), 7.
34 (1/2H, dd, $J=8.6, 2.7\text{ Hz}$), 7.36 (1/2H, d
d, $J=8.6, 2.7\text{ Hz}$), 7.42 (1/2H, s), 7.43 (1/
2H, s), 7.74 (1/2H, s), 8.01 (1/2H, d, $J=8.$
20 6 Hz), 8.02 (1/2H, d, $J=8.6\text{ Hz}$), 8.46 (1H, d,
 $J=2.7\text{ Hz}$), 8.58 (1/2H, dd, $J=2.7, 1.6\text{ Hz}$),
8.60 (1/2H, dd, $J=2.7, 1.6\text{ Hz}$), 8.67 (1/2H,
d, $J=2.7\text{ Hz}$), 8.68 (1/2H, d, $J=2.7\text{ Hz}$), 9.5
9 (1/2H, d, $J=1.6\text{ Hz}$), 9.62 (1/2H, d, $J=1.6$
25 Hz), 10.47 (1/2H, brs), 10.61 (1/2H, brs)

ESI-MS (m/e): 478 [M+H]

実施例202

5 - (2-フルオロフェノキシ) - 2 - (1H-ピラゾール-3-イル) -
6 - (6-メタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイ
ミダゾール

実施例200で得られた4-(2-フルオロフェノキシ)-5-(6-メ
 5 タンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン
 15 mgのジメチルホルムアミド0.5ml溶液に、1H-ピラゾール-3-
 カルボキサアルデヒド3.9mgを加え、反応液を90度にて30分間撹拌し
 た。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (K i
 e s e l g e l T M 6 0 F 2 5 4、A r t 5 7 4 4 (メルク社製)、クロロホ
 10 ルム/メタノール=9/1) にて精製し、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.20 (3H, s), 6.94-6.99 (1
 H, m), 7.01-7.15 (4H, m), 7.25-7.65 (2H, m), 7.31 (1H, dd, $J=8.9, 2.7\text{ Hz}$), 7.66 (1H,
 d, $J=2.3\text{ Hz}$), 7.98 (1H, d, $J=8.9\text{ Hz}$), 8.40
 15 (1H, d, $J=2.7\text{ Hz}$)

ESI-MS (m/e): 466 $[\text{M}+\text{H}]$

実施例203

5 - (2-フルオロフェノキシ) - 2 - (1-メチル-1H-ピラゾール-
 20 3-イル) - 6 - (6-メタンスルホニル-ピリジン-3-イルオキシ) - 1
H-ベンズイミダゾール

実施例200で得られた4-(2-フルオロフェノキシ)-5-(6-メ
 タンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン
 15 mgのジメチルホルムアミド0.5ml溶液に、1-メチル-1H-ピラ
 25 ゴール-3-カルボン酸4.3mg、ヒドロキシベンゾトリアゾール6.0m
 g、及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・
 一塩酸塩8.5mgを加え、反応液を室温にて一終夜撹拌した。反応液を、ク
 ロロホルムにて希釈し、水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒
 を減圧留去し、得られた残渣にp-トルエンスルホン酸3mgを加え、反応液

を120度にて2時間攪拌した。反応液を、酢酸エチルにて希釈し、水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、残渣を分取用薄層クロマトグラフィー (Kieselgel TM 60 F 254, Art 5744 (メルク社製)、クロロホルム/メタノール=15/1) にて精製し、表題化合物を白色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 3.19 (3H, s), 3.97 (3H, s), 6.94–7.00 (1H, m), 6.99 (1/2H, brs), 7.00–7.14 (4H, m), 7.27–7.33 (1H, m), 7.30 (1/2H, brs), 7.40 (1/2H, brs), 7.46 (1H, d, $J=2.4\text{ Hz}$), 7.65 (1/2H, brs), 7.98 (1H, d, $J=8.8\text{ Hz}$), 8.42 (1H, d, $J=2.7\text{ Hz}$)

ESI-MS (m/e): 480 $[\text{M}+\text{H}]$

実施例204

15 5-(2-クロロフェノキシ)-2-ピリジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール
(工程1)

4-(2-クロロフェノキシ)-5-(6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミンの合成

20 実施例196 (工程3) で得られた5-フルオロ-4-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロフェニルアミン、及び2-クロロフェノールを用いて、実施例196 (工程4) ~ (工程5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

25 (工程2)

5-(2-クロロフェノキシ)-2-ピリジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

(工程1)で得られた4-(2-クロロフェノキシ)-5-(6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン35mgのメタノール1ml溶液に、アニリン及びピリジン-2-カルボキサアルデヒド(1:1)の1Mメタノール溶液0.26mlを加え、反応液を60度にて一終夜攪拌した。溶媒を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー[ODS-AS-360-CC(YMC社製)移動相:水-アセトニトリル-0.1%トリフルオロ酢酸]にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ: 3.17 (3H, s), 6.92 (1H, d, J=8.0 Hz), 7.07 (1H, t, J=8.0 Hz), 7.22 (1H, t, J=8.0 Hz), 7.26-7.66 (4H, m), 7.66-7.80 (1H, brs), 7.90-8.08 (2H, m), 8.29 (1H, d, J=8.0 Hz), 8.31 (1H, d, J=2.4 Hz), 8.72 (1H, s)

ESI-MS (m/e): 493 [M+H]

実施例205

5-(2-クロロフェノキシ)-2-ピラジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例204(工程1)で得られた4-(2-クロロフェノキシ)-5-(6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン38mgのN-メチルピロリジノン0.5ml溶液に、メチルピラジン-2-イミデート(Pyrazine-2-carboximidic acid methyl ester)15mg及びメタンスルホン酸0.0065mlを加え、反応液を120度にて20分間攪拌した。反応液を逆相中圧液体クロマトグラフィー[ODS-AS-360-CC(YMC社製)移動相:水-アセトニトリル-0.1%トリフルオロ酢酸]にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水

硫酸ナトリウムで乾燥した。溶媒を減圧留去することにより、表題化合物を黄色固体として得た。

^1H NMR (CD_3OD) δ : 3.20 (3H, s), 6.97 (1H, d, J = 7.8 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.26 (1H, t, J = 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.48 (1H, dd, J = 8.6, 2.3 Hz), 7.60–7.82 (2H, m), 8.02 (1H, d, J = 8.6 Hz), 8.35 (1H, d, J = 2.3 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.48 (1H, s)
ESI-MS (m/e): 494 [M+H]

10

実施例206

5-(2-トリフルオロメチルフェノキシ)-2-ピリジン-2-イル-6-(6-メタンスルホニルピリジン-3-イルオキシ)-1H-ベンズイミダゾール

15 実施例196 (工程3) で得られた5-フルオロ-4-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ニトロフェニルアミン、及び2-トリフルオロメチルフェノールを用いて、実施例196 (工程4) 乃至 (工程6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

20 ^1H NMR (CD_3OD) δ : 3.17 (3H, s), 6.93–6.98 (1H, m), 7.21 (1H, t, J = 7.4 Hz), 7.40–7.81 (6H, m), 7.97–8.05 (2H, m), 8.24–8.39 (2H, m), 8.73–8.87 (1H, m)
ESI-MS (m/e): 527 [M+H]

25

実施例207

5-(2-トリフルオロメチルフェノキシ)-2-ピラジン-2-イル-6-(6-メタンスルホニルピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 206 で得られた 4-(2-トリフルオロメチルフェノキシ)-
5-(6-メタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1,
2-ジアミン、及びメチルピラジン-2-イミデートを用いて、実施例 20
5 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
5 により、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.17 (3H, s), 6.97 (1H, d, J
= 7.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.46 (1H,
dd, J = 8.6, 2.3 Hz), 7.54 (1H, t, J = 7.8 Hz),
7.44-7.60 (1H, m), 7.65 (1H, d, J = 7.8 Hz),
10 7.84-7.86 (1H, m), 8.01 (1H, d, J = 8.6 Hz),
8.31 (1H, d, J = 2.3 Hz), 8.73 (1H, d, J = 2.3 Hz),
8.80 (1H, d, J = 2.3 Hz), 9.50 (1H, s)
ESI-MS (m/e): 528 [M+H]

15 実施例 208

5-(3-トリフルオロメチルフェノキシ)-2-ピリジン-2-イル-
6-(6-メタンスルホニルピリジン-3-イルオキシ)-1H-ベンズイ
ミダゾール

実施例 196 (工程 3) で得られた 5-フルオロ-4-(6-メタンスルホ
20 ニルピリジン-3-イルオキシ)-2-ニトロフェニルアミン、及び 3-
トリフルオロメチルフェノールを用いて、実施例 196 (工程 4) ~ (工程
6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.20 (3H, s), 7.00-7.15 (2
25 H, m), 7.37 (1H, d, J = 7.8 Hz), 7.45-7.55 (3
H, m), 7.66 (1H, d, J = 10.0 Hz), 7.76 (1H, br
s), 7.99-8.04 (2H, m), 8.30-8.35 (2H, m),
8.77 (1H, d, J = 2.7 Hz)
ESI-MS (m/e): 527 [M+H]

実施例 209

5-（4-トリフルオロメチルフェノキシ）-2-ピリジン-2-イル-6-（6-メタンスルホニルピリジン-3-イルオキシ）-1H-ベンズイミダゾール

実施例 196（工程 3）で得られた 5-フルオロ-4-（6-メタンスルホニルピリジン-3-イルオキシ）-2-ニトロフェニルアミン、及び 4-トリフルオロメチルフェノールを用いて、実施例 196（工程 4）乃至（工程 6）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.20 (3H, s), 6.98 (2H, d, $J=8.6\text{ Hz}$), 7.46-7.77 (4H, m), 7.60 (2H, d, $J=8.6\text{ Hz}$), 8.00-8.04 (2H, m), 8.31 (1H, d, $J=3.1\text{ Hz}$), 8.34 (1H, d, $J=8.2\text{ Hz}$), 8.78 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 527 [$M+H$]

実施例 210

5-（2-ジフルオロメチルフェノキシ）-2-ピリジン-2-イル-6-（6-メタンスルホニルピリジン-3-イルオキシ）-1H-ベンズイミダゾール

実施例 196（工程 3）で得られた 5-フルオロ-4-（6-メタンスルホニルピリジン-3-イルオキシ）-2-ニトロフェニルアミン、及び 2-ジフルオロメチルフェノールを用いて、実施例 196（工程 4）乃至（工程 6）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.17 (3H, s), 6.70 (1H, t, $J=55.2\text{ Hz}$), 6.87 (1H, d, $J=7.4\text{ Hz}$), 7.18 (1H, t, $J=7.4\text{ Hz}$), 7.40-7.46 (2H, m), 7.50-7.5

9 (3H, m), 7.59–7.82 (1H, m), 7.98–8.04 (2H, m), 8.27–8.35 (2H, m), 8.76 (1H, brs)

ESI-MS (m/e) : 509 [M+H]

5 実施例211

5-(2-フルオロピリジン-3-イルオキシ)-6-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例196(工程3)で得られた5-フルオロ-4-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニルアミン、及び
10 ジャーナル オブ メディシナルケミストリー (Journal of Medicinal Chemistry)、1999年 第42巻、12号、2251頁–2259頁に記載されている方法にて合成した2-フルオロ-ピリジン-3-オールを用いて、実施例196(工程4)乃至(工程6)と同様の
15 の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CDCl₃) δ : 3.21 (3H, s), 7.11–7.17 (1H, m), 7.22 (1/2H, s), 7.29–7.36 (2H, m), 7.29–7.36 (1/2H, m), 7.40–7.43 (1H, s), 7.5
20 3 (1/2H, s), 7.72 (1/2H, s), 7.88–7.93 (1H, m), 7.93–7.96 (1H, m), 7.99–8.03 (1H, m), 8.37–8.41 (2H, m), 8.65–8.67 (1H, m), 10.78 (1/2H, brs), 10.82 (1/2H, brs)

ESI-MS (m/e) : 478 [M+H]

25

実施例212

5-(2-フルオロピリジン-3-イルオキシ)-6-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例 2 1 1 で得られた 4 - (2 - フルオロ - ピリジン - 3 - イルオキシ) - 5 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - ベンゼン - 1, 2 - ジアミン、及びピラジン - 2 - カルボン酸を用いて、実施例 1 9 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CDCl_3) δ : 3. 2 1 (3H, s), 7. 1 4 - 7. 1 9 (1H, m), 7. 2 3 (1/2H, s), 7. 2 6 - 7. 4 0 (2H, m), 7. 4 6 (1/2H, s), 7. 5 4 (1/2H, s), 7. 5 6 (1/2H, s), 7. 9 6 - 8. 0 0 (1H, m), 8. 0 3 (1H, dd, $J=8. 6, 3. 9\text{ Hz}$), 8. 4 1 (1H, dd, $J=2. 7, 1. 6\text{ Hz}$), 8. 6 2 (1H, ddd, $J=4. 7, 2. 7, 1. 6\text{ Hz}$), 8. 6 9 - 8. 7 1 (1H, m), 9. 6 2 (1H, dd, $J=6. 3, 1. 6\text{ Hz}$), 10. 4 8 (1/2H, brs), 10. 5 6 (1/2H, brs)
ESI-MS (m/e): 479 [$M+H$]

15

実施例 2 1 3

5 - (2 - フルオロピリジン - 3 - イルオキシ) - 2 - (1H - ピラゾール - 3 - イル) - 6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベンズイミダゾール

20 実施例 2 1 1 で得られた 4 - (2 - フルオロ - ピリジン - 3 - イルオキシ) - 5 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - ベンゼン - 1, 2 - ジアミン、及び 1H - ピラゾール - 3 - カルボキサルデヒドを用いて、実施例 2 0 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

25 ^1H NMR (CDCl_3) δ : 3. 2 1 (3H, s), 7. 0 8 (1H, d, $J=2. 3\text{ Hz}$), 7. 0 9 - 7. 1 9 (1H, m), 7. 1 9 - 7. 4 9 (4H, m), 7. 7 1 (1H, d, $J=2. 3\text{ Hz}$), 7. 8 8 - 7. 9 6 (1H, m), 7. 9 7 - 8. 0 3 (1H, m), 8. 3 6 (1H, d, $J=2. 7\text{ Hz}$)

ESI-MS (m/e) : 467 [M+H]

実施例 214

5 5-(2-フルオロピリジン-3-イルオキシ)-2-(1-メチル-1H-
ピラゾール-3-イル)-6-(6-メタンスルホニル-ピリジン-3-イル
オキシ)-1H-ベンズイミダゾール

実施例 211 で得られた 4-(2-フルオロ-ピリジン-3-イルオキシ)-5-(6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及び 1-メチル-1H-ピラゾール-3-カルボン酸
10 を用いて、実施例 203 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 3.20 (3H, s), 4.00 (3H, s),
7.00 (1H, d, $J=2.4\text{ Hz}$), 7.10-7.16 (1H, m),
7.19 (1/2H, brs), 7.26-7.33 (2H, m), 7.35
15 (1/2H, brs), 7.48 (1H, d, $J=2.4\text{ Hz}$), 7.52
(1/2H, brs), 7.67 (1/2H, brs), 7.91-7.94
(1H, m), 8.00 (1H, d, $J=8.6\text{ Hz}$), 8.37 (1H, d,
 $J=2.5\text{ Hz}$), 10.13 (1H, brs)

ESI-MS (m/e) : 481 [M+H]

20

実施例 215

5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(6-メ
タンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1
H-ベンズイミダゾール

25 実施例 196 (工程 3) で得られた 5-フルオロ-4-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニルアミン、及び参考例 2 で得られた 2-ジフルオロメトキシ-ピリジン-3-オールを用いて、実施例 196 (工程 4) 乃至 (工程 6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (DMSO- d_6) δ : 3.22 (3H, s), 7.19–7.27 (1H, m), 7.29–7.86 (6H, m), 7.95–8.07 (3H, m), 8.33–8.35 (1H, m), 8.45–8.48 (1H, m), 8.77 (1H, s).

5 ESI-MS (m/e): 526 [M+H]

実施例216

5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(6-メ
タンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1

10 H-ベンズイミダゾール

実施例215で得られた4-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-5-(6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及びメチルピラジン-2-イミデートを用いて、実施例205と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (DMSO- d_6) δ : 3.20 (3H, s), 7.21 (1H, d, $J=7.8, 4.9\text{ Hz}$), 7.30–7.90 (4H, m), 7.62 (1H, t, $J=72.6\text{ Hz}$), 7.94 (1H, d, $J=8.8\text{ Hz}$), 7.97 (1H, d, $J=4.8\text{ Hz}$), 8.45 (1H, d, $J=2.7\text{ Hz}$), 8.77–8.83 (2H, m), 9.48 (1H, s)

20 ESI-MS (m/e): 527 [M+H]

実施例217

5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(6-メ
 25 タンスルホニル-ピリジン-3-イルオキシ)-2-(1-メチル-1H-ピ
ラゾール-3-イル)-1H-ベンズイミダゾール

実施例215で得られた4-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-5-(6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及び1-メチル-1H-ピラゾール-3-カルボ

ン酸を用いて、実施例 203 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ : 3.22 (3H, s), 4.00 (3H, s), 6.88 (1H, d, $J=2.2\text{ Hz}$), 7.17–7.82 (6H, m), 7.90–7.99 (3H, m), 8.42–8.45 (1H, m)
ESI-MS (m/e) : 529 [M+H]

実施例 218

5 – (2-シアノピリジン-3-イルオキシ) – 6 – (6-メタンスルホニル
10. ピリジン-3-イルオキシ) – 2-ピリジン-2-イル-1H-ベンズイミダ
ゾール

(工程 1)

4 – (6-メタンスルホニル-ピリジン-3-イルオキシ) – 2-ニトロ-
5 – (1-オキシ-ピリジン-3-イルオキシ) – フェニルアミンの合成

15 実施例 196 (工程 3) で得られた 5-フルオロ-4 – (6-メタンスルホ
ニル-ピリジン-3-イルオキシ) – 2-ニトロ-フェニルアミン、及び 1-
オキシ-ピリジン-3-オールを用いて、実施例 196 (工程 4) と同様の方
法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化
合物を得た。

20 (工程 2)

4 – (6-メタンスルホニル-ピリジン-3-イルオキシ) – 2-ニトロ-
5 – (2-シアノ-ピリジン-3-イルオキシ) – フェニルアミンの合成

4 – (6-メタンスルホニル-ピリジン-3-イルオキシ) – 2-ニトロ-
5 – (1-オキシ-ピリジン-3-イルオキシ) – フェニルアミン 216 mg
25 のアセトニトリル 6 ml 溶液に、トリメチルシリルニトリル 0.90 ml、及
びトリエチルアミン 0.90 ml を加えた後、反応液を加熱還流下、一終夜攪
拌した。溶媒を減圧留去した後、1, 1, 1, 3, 3, 3-ヘキサメチルジシ
ラザンを加え、反応液を加熱還流下、1 時間攪拌した。反応液をシリカゲルカ

ラムクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝30／1）にて精製し、表題化合物を得た。

（工程3）

5-（2-シアノピリジン-3-イルオキシ）-6-（6-メタンスルホニルピリジン-3-イルオキシ）-2-ピリジン-2-イル-1H-ベンズイミダゾールの製造

4-（6-メタンスルホニルピリジン-3-イルオキシ）-2-ニトロ-5-（2-シアノピリジン-3-イルオキシ）-フェニルアミンを用いて、実施例196（工程5）及び（工程6）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。
¹HNMR (CDCl₃) δ: 3.22 (3/2H, s), 3.23 (3/2H, s), 7.18-7.23 (2H, m), 7.40-7.48 (2H, m), 7.50 (1H, s), 7.76-7.78 (1H, m), 7.91-7.95 (1H, m), 8.03-8.06 (1H, m), 8.20-8.23 (1H, m), 8.37-8.44 (2H, m), 8.58-8.67 (1H, m), 11.04 (1H, brs)
 ESI-MS (m/e): 485 [M+H]

実施例219

5-（2-シアノピリジン-3-イルオキシ）-6-（6-メタンスルホニルピリジン-3-イルオキシ）-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例218（工程3）で得られた4-（2-シアノピリジン-3-イルオキシ）-5-（6-メタンスルホニルピリジン-3-イルオキシ）-ベンゼン-1,2-ジアミン、及びピラジン-2-カルボン酸を用いて、実施例197と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

¹HNMR (CDCl₃) δ: 3.23 (3/2H, s), 3.24 (3/2H, s), 7.21-7.26 (2H, m), 7.42-7.48 (1H, m),

7. 55 (1H, d, $J=1.2$ Hz), 7. 80 (1/2H, s), 7. 8
2 (1/2H, s), 8. 04 (1/2H, s), 8. 06 (1/2H, s),
8. 19-8. 21 (1H, m), 8. 41 (1H, dd, $J=4.5, 1.$
2 Hz), 8. 65 (1H, dd, $J=3.9, 2.3$ Hz), 8. 73 (1
5 H, d, $J=2.3$ Hz), 9. 65 (1H, d, $J=1.2$ Hz), 10.
99 (1H, brs)

ESI-MS (m/e): 486 [M+H]

実施例 220

10 5-(2-シアノピリジン-3-イルオキシ)-2-(1H-ピラゾール-
3-イル)-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-1
H-ベンズイミダゾール

実施例 218 (工程 3) で得られた 4-(2-シアノピリジン-3-イルオ
キシ)-5-(6-メタンスルホニル-ピリジン-3-イルオキシ)-ベンゼ
15 ン-1, 2-ジアミン、及び 1H-ピラゾール-3-カルボキサアルデヒドを
用いて、実施例 202 と同様の方法、これに準じた方法又はこれらと常法とを
組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CDCl_3) δ : 3. 22 (3H, s), 7. 12 (1H, d, J
= 2. 3 Hz), 7. 17-7. 25 (2H, m), 7. 40-7. 48 (2
20 H, m), 7. 71-7. 74 (1H, m), 7. 72 (1H, d, $J=2.$
3 Hz), 8. 00-8. 03 (1H, m), 8. 17-8. 21 (1H,
m), 8. 38-8. 41 (1H, m)

ESI-MS (m/e): 474 [M+H]

25 実施例 221

5-(2-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(6-エタ
ンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

(工程 1)

3-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-フェニルアミンの合成

実施例196(工程1)で得られた(3-フルオロ-4-ヒドロキシ-フェニル)-カルバミン酸 tert-ブチルエステル10.0gのジメチルホルムアミド150ml溶液に、5-クロロ-2-エタンスルホニル-ピリジン10.9g、及び炭酸セシウム21.6gを加え、反応液を100度にて3時間攪拌した。溶媒を減圧留去した後、クロロホルムにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=1/9)にて精製し、粗生成物を得た。得られた粗生成物を4規定塩酸-ジオキサンに溶解し、室温にて1時間攪拌した。溶媒を減圧留去した後、クロロホルムにて希釈し、水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=1/9)にて精製し、表題化合物を得た。

15 (工程2)

5-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニルアミンの合成

3-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-フェニルアミン10.5gのトリフルオロ酢酸100ml溶液に、硝酸カリウム3.8gを加え、反応液を室温にて1時間攪拌した後、溶媒を減圧留去した。残渣を酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=1/2)にて精製し、表題化合物を得た。

25 (工程3)

5-(2-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

- 5-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロフェニルアミン150mgのN-メチルピロリジノン3ml溶液に、2-ヒドロキシベンゾニトリル60mg、及び炭酸カリウム70mgを加え、反応液を90度にて5時間攪拌した。反応液に水を加えた後、沈殿物を濾取することにより、粗生成物を得た。得られた粗生成物のメタノール5ml溶液に、展開ラネーニッケル触媒10mg、及びヒドラジン・一水和物0.12mlを加え、反応液を1時間攪拌した。触媒を濾去後、溶媒を減圧留去し、粗生成物160mgを得た。得られた粗生成物35mgのメタノール3ml溶液に、アニリン及びピリジン-2-カルボキサルデヒド(1:1)の1Mメタノール溶液0.20mlを加え、反応液を80度にて一終夜攪拌した。溶媒を減圧留去した後、得られた残渣を分取用薄層クロマトグラフィー(Kieselgel TM60F254、Art 5744 (メルク社製)、クロロホルム/メタノール=15/1)にて精製し、表題化合物を黄色固体として得た。
- $^1\text{H NMR}$ (CD_3OD) δ : 1.27 (3H, t, $J=7.4\text{ Hz}$), 3.37 (2H, q, $J=7.4\text{ Hz}$), 6.91 (1H, d, $J=7.8\text{ Hz}$), 7.19 (1H, t, $J=7.8\text{ Hz}$), 7.43 (1H, d, $J=7.8\text{ Hz}$), 7.50-7.60 (2H, m), 7.60-7.90 (3H, m), 7.99-8.04 (2H, m), 8.26 (1H, s), 8.34 (1H, d, $J=7.8\text{ Hz}$), 8.77 (1H, s)
- ESI-MS (m/e): 498 $[\text{M}+\text{H}]$

実施例 222

5-(2-シアノフェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 25 実施例 221 (工程 3) で得られた 4-(2-シアノフェノキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及びメチルピラジン-2-イミデートを用いて、実施例 205 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

^1H NMR (CD_3OD) δ : 1.28 (3H, t, $J=7.6\text{ Hz}$), 3.38 (2H, q, $J=7.6\text{ Hz}$), 6.94 (1H, d, $J=7.6\text{ Hz}$), 7.21 (1H, t, $J=7.6\text{ Hz}$), 7.45 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 7.58 (1H, td, $J=7.6, 1.8\text{ Hz}$), 7.66 (1H, d, $J=7.6\text{ Hz}$), 7.68–7.90 (2H, m), 8.03 (1H, d, $J=8.6\text{ Hz}$), 8.28 (1H, d, $J=2.7\text{ Hz}$), 8.75 (1H, d, $J=2.0\text{ Hz}$), 8.82 (1H, dd, $J=2.0, 1.2\text{ Hz}$), 9.54 (1H, d, $J=1.2\text{ Hz}$)

ESI-MS (m/e): 499 $[\text{M}+\text{H}]$

10

実施例 223

5-(2-フルオロフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 221 (工程 2) で得られた 5-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロフェニルアミン、及び 2-フルオロフェノールを用いて、実施例 221 (工程 3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CD_3OD) δ : 1.18–1.24 (3H, m), 3.02–3.41 (2H, m), 6.97–7.40 (5H, m), 7.47–7.77 (3H, m), 7.96–8.04 (2H, m), 8.30 (1H, d, $J=7.8\text{ Hz}$), 8.39–8.42 (1H, m), 8.73–8.78 (1H, m)

ESI-MS (m/e): 491 $[\text{M}+\text{H}]$

25

実施例 224

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 2 2 3 で得られた 4 - (2 - フルオロ - フェノキシ) - 5 - (6 - エ
タンスルホニル - ピリジン - 3 - イルオキシ) - ベンゼン - 1, 2 - ジアミン、
及びメチル ピラジン - 2 - イミデートを用いて、実施例 2 0 5 と同様の方法、
これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
5 を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1. 2 2 (3H, t, $J=7.4\text{ Hz}$), 3. 3
8 (2H, q, $J=7.4\text{ Hz}$), 7. 5 2 (1H, dd, $J=3.1, 8.6\text{ Hz}$), 7. 0 0 - 7. 8 0 (6H, m), 8. 0 4 (1H, d, $J=8.6\text{ Hz}$), 8. 4 2 (1H, d, $J=3.1\text{ Hz}$), 8. 7 2 (1H, s),
10 8. 7 9 (1H, s), 9. 4 9 (1H, s)

ESI-MS (m/e) : 492 [M+H]

実施例 2 2 5

5 - (2 - フルオロ - フェノキシ) - 2 - (1H - ピラゾール - 3 - イル) -
15 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベンズイ
ミダゾール

実施例 2 2 3 で得られた 4 - (2 - フルオロ - フェノキシ) - 5 - (6 - エ
タンスルホニル - ピリジン - 3 - イルオキシ) - ベンゼン - 1, 2 - ジアミン、
及び 1H - ピラゾール - 3 - カルボキサアルデヒドを用いて、実施例 2 0 2 と
20 同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1. 2 2 (3H, t, $J=7.4\text{ Hz}$), 3. 3
0 - 3. 4 2 (2H, m), 6. 8 8 (1H, d, $J=1.6\text{ Hz}$), 6. 9
9 - 7. 0 4 (1H, m), 7. 0 7 - 7. 2 0 (3H, m), 7. 2 2 - 7.
25 4 3 (1H, m), 7. 4 9 (1H, dd, $J=7.8, 3.1\text{ Hz}$), 7.
5 6 - 7. 6 8 (1H, m), 7. 8 3 (1H, d, $J=1.6\text{ Hz}$), 8.
0 2 (1H, d, $J=7.8\text{ Hz}$), 8. 3 9 (1H, d, $J=3.1\text{ Hz}$)

ESI-MS (m/e) : 480 [M+H]

実施例 2 2 6

5-(2, 3-ジフルオロフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 5 実施例 2 2 1 (工程 2) で得られた 5-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロフェニルアミン、及び 2, 3-ジフルオロフェノールを用いて、実施例 2 2 1 (工程 3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

- 10 $^1\text{H NMR}$ (CDCl_3) δ : 1. 29 (3H, t, $J=7.4\text{ Hz}$), 3. 38 (2H, q, $J=7.4\text{ Hz}$), 6. 69-6. 75 (1H, m), 6. 91-7. 02 (2H, m), 7. 20 (1/2H, s), 7. 27-7. 34 (1H, m), 7. 37-7. 47 (1H, m), 7. 41 (1/2H, s), 7. 53 (1/2H, s), 7. 72 (1/2H, s), 7. 87-7. 92 (1H, m), 8. 00 (1/2H, d, $J=8.7\text{ Hz}$), 8. 01 (1/2H, d, $J=8.7\text{ Hz}$), 8. 36-8. 41 (1H, m), 8. 42 (1H, d, $J=2.7\text{ Hz}$), 8. 63-8. 67 (1H, m), 10. 75 (1/2H, brs), 10. 80 (1/2H, brs)

ESI-MS (m/e): 509 $[\text{M}+\text{H}]$

20

実施例 2 2 7

5-(2, 3-ジフルオロフェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 25 実施例 2 2 6 で得られた 4-(2, 3-ジフルオロフェノキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及びピラジン-2-カルボン酸を用いて、実施例 1 9 7 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

^1H NMR (CDCl_3) δ : 1.29 (3H, t, $J=7.4\text{ Hz}$)、3.38 (1H, q, $J=7.4\text{ Hz}$)、3.39 (1H, q, $J=7.4\text{ Hz}$)、6.72–6.78 (1H, m)、6.92–7.05 (2H, m)、7.22 (1/2H, s)、7.33 (1/2H, dd, $J=8.8, 2.7\text{ Hz}$)、
 5 7.34 (1/2H, dd, $J=8.8, 2.7\text{ Hz}$)、7.45 (1/2H, s)、7.53 (1/2H, s)、7.75 (1/2H, s)、8.01 (1/2H, d, $J=8.8\text{ Hz}$)、8.02 (1/2H, d, $J=8.8\text{ Hz}$)、8.43 (1H, d, $J=2.7\text{ Hz}$)、8.60 (1/2H, dd, $J=2.5, 1.6\text{ Hz}$)、8.62 (1/2H, dd, $J=2.5, 1.6\text{ Hz}$)、
 10 8.69 (1/2H, d, $J=2.5\text{ Hz}$)、8.70 (1/2H, d, $J=2.5\text{ Hz}$)、9.61 (1/2H, d, $J=1.6\text{ Hz}$)、9.63 (1/2H, d, $J=1.6\text{ Hz}$)、10.52 (1/2H, brs)、10.62 (1/2H, brs)

ESI-MS (m/e): 510 $[\text{M}+\text{H}]$

15

実施例 228

5-(2,3-ジフルオロフェノキシ)-2-(1-メチル-1H-ピラゾール-3-イル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

20 実施例 226 で得られた 4-(2,3-ジフルオロフェノキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及び 1-メチル-1H-ピラゾール-3-カルボン酸を用いて、実施例 203 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

25 ^1H NMR (CDCl_3) δ : 1.29 (3H, t, $J=7.4\text{ Hz}$)、3.37 (1H, q, $J=7.4\text{ Hz}$)、3.38 (1H, q, $J=7.4\text{ Hz}$)、3.97 (2H, s)、3.98 (1H, s)、6.65–6.75 (1/3 H, m)、6.87 (1/2H, brs)、6.89–7.01 (3H, m)、7.10–7.19 (1H, m)、7.26–7.38 (1H, m)、7.3

0 (1/2H, s), 7.45 (2/3H, d, J=2.3Hz), 7.47
 (1/3H, d, J=2.3Hz), 7.50-7.53 (1/6H, m),
 7.62-7.67 (1/2H, m), 7.95-8.05 (1H, m), 8.
 39 (1/3H, d, J=2.5Hz), 8.54 (2/3H, d, J=2.
 5 Hz), 10.00-10.25 (1H, m)
 ESI-MS (m/e) : 512 [M+H]

実施例 229

5- (2, 4-ジフルオロフェノキシ) -2-ピリジン-2-イル-6-
 10 (6-エタンスルホニル-ピリジン-3-イルオキシ) -1H-ベンズイミダ
 ゴール

実施例 221 (工程 2) で得られた 5-フルオロ-4- (6-エタンスルホ
 ニル-ピリジン-3-イルオキシ) -2-ニトロフェニルアミン、及び 2,
 4-ジフルオロフェノールを用いて、実施例 221 (工程 3) と同様の方法、
 15 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
 を無色固体として得た。

¹HNMR (CDCl₃) δ : 1.29 (3H, t, J=7.4Hz), 3.3
 7 (1H, q, J=7.4Hz), 3.38 (1H, q, J=7.4Hz),
 6.81-6.95 (2H, m), 6.95-7.05 (1H, m), 7.0
 20 6 (1/2H, s), 7.33 (1/2H, s), 7.32 (1/2H, dd,
 J=8.6, 2.7Hz), 7.34 (1/2H, dd, J=8.6, 2.7
 Hz), 7.37-7.41 (1H, m), 7.40 (1/2H, s), 7.
 70 (1/2H, s), 7.86-7.91 (1H, m), 8.00 (1/2
 H, d, J=8.6Hz), 8.01 (1/2H, d, J=8.6Hz), 8.
 25 34-8.39 (1H, m), 8.46 (1H, d, J=2.7Hz), 8.
 62-8.67 (1H, m), 10.67 (1/2H, brs), 10.76
 (1/2H, brs)

ESI-MS (m/e) : 509 [M+H]

実施例 230

5-(2, 4-ジフルオロフェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 5 実施例 229 で得られた 4-(2, 4-ジフルオロフェノキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及びピラジン-2-カルボン酸を用いて、実施例 197 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

- 10 $^1\text{H NMR}$ (CDCl_3) δ : 1.30 (3H, t, $J=7.4\text{ Hz}$), 3.38 (1H, q, $J=7.4\text{ Hz}$), 3.39 (1H, q, $J=7.4\text{ Hz}$), 6.82-6.95 (2H, m), 6.98-7.05 (1H, m), 7.08 (1/2H, s), 7.34 (1/2H, dd, $J=8.6, 2.7\text{ Hz}$), 7.35 (1/2H, dd, $J=8.6, 2.7\text{ Hz}$), 7.38 (1/2H, s), 7.44 (1/2H, s), 7.74 (1/2H, s), 8.02 (1/2H, d, $J=8.6\text{ Hz}$), 8.03 (1/2H, d, $J=8.6\text{ Hz}$), 8.46 (1/2H, d, $J=2.7\text{ Hz}$), 8.47 (1/2H, d, $J=2.7\text{ Hz}$), 8.58 (1/2H, dd, $J=2.7, 1.6\text{ Hz}$), 8.60 (1/2H, dd, $J=2.7, 1.6\text{ Hz}$), 8.67 (1/2H, d, $J=2.7\text{ Hz}$), 8.68 (1/2H, d, $J=2.7\text{ Hz}$), 9.59 (1/2H, d, $J=1.6\text{ Hz}$), 9.61 (1/2H, d, $J=1.6\text{ Hz}$), 10.54 (1/2H, brs), 10.69 (1/2H, brs)
- 15 ESI-MS (m/e): 510 [$M+H$]

25 実施例 231

5-(2, 4-ジフルオロフェノキシ)-2-(1-メチル-1H-ピラゾール-3-イル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 229 で得られた 4-(2, 4-ジフルオロフェノキシ)-5-(6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及び 1-メチル-1H-ピラゾール-3-カルボン酸を用いて、実施例 203 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.28 (3H, t, $J=7.4\text{ Hz}$), 3.38 (2H, q, $J=7.4\text{ Hz}$), 3.98 (3H, s), 6.78-6.85 (1H, m), 6.85-6.93 (1H, m), 6.93-6.98 (1H, m), 6.93-6.98 (1/2H, m), 6.99 (1H, d, $J=2.3\text{ Hz}$), 7.02 (1/2H, brs), 7.27-7.34 (1H, m), 7.36 (1/2H, brs), 7.46 (1H, d, $J=2.3\text{ Hz}$), 7.64 (1/2H, brs), 7.99 (1H, d, $J=8.6\text{ Hz}$), 8.43 (1H, d, $J=2.7\text{ Hz}$), 10.19 (1/2H, brs), 10.29 (1/2H, brs)

ESI-MS (m/e): 512 $[\text{M}+\text{H}]$

実施例 232

5-(2, 5-ジフルオロフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニルピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 221 (工程 2) で得られた 5-フルオロ-4-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ニトロフェニルアミン、及び 2, 5-ジフルオロフェノールを用いて、実施例 221 (工程 3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.23 (3H, t, $J=7.4\text{ Hz}$), 3.38 (2H, q, $J=7.4\text{ Hz}$), 6.76-6.89 (2H, m), 7.15-7.24 (1H, m), 7.49-7.55 (3H, m), 7.71 (1H, s), 8.01 (1H, td, $J=7.4, 2.3\text{ Hz}$), 8.04 (1

H, d, $J=7.4\text{ Hz}$), 8.32 (1H, d, $J=7.4\text{ Hz}$), 8.40 (1H, d, $J=2.3\text{ Hz}$), 8.77 (1H, d, $J=4.3\text{ Hz}$)

ESI-MS (m/e): 509 [M+H]

5 実施例233

5-(2, 5-ジフルオロフェノキシ)-2-ピリジン-1-オキシド-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例232で得られた5-(2, 5-ジフルオロフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール7.5mgのクロロホルム1.5ml溶液に、
 10 m-クロロ過安息香酸7.5mgを加えた後、反応液を45度にて1時間攪拌した。溶媒を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC社製) 移動相: 水-アセトニトリル-
 15 0.1%トリフルオロ酢酸] にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.23 (3H, t, $J=7.4\text{ Hz}$), 3.38 (2H, q, $J=7.4\text{ Hz}$), 6.78-6.90 (2H, m), 7.20 (1H, td, $J=9.8, 5.1\text{ Hz}$), 7.52 (1H, dd, $J=6.6, 3.1\text{ Hz}$), 7.56 (1H, s), 7.62 (1H, t, $J=8.2\text{ Hz}$), 7.73 (1H, t, $J=8.2\text{ Hz}$), 7.78 (1H, s), 8.04 (1H, d, $J=8.2\text{ Hz}$), 8.41 (1H, d, $J=3.1\text{ Hz}$), 8.51 (1H, d, $J=6.6\text{ Hz}$), 8.64 (1H, d, $J=8.2\text{ Hz}$)
 25 z)

ESI-MS (m/e): 525 [M+H]

実施例234

5 - (2, 5 - ジフルオロ - フェノキシ) - 2 - ピラジン - 2 - イル - 6 -
(6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベンズイミダ
ゾール

実施例 232 で得られた 4 - (2, 5 - ジフルオロ - フェノキシ) - 5 -
 5 (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - ベンゼン - 1, 2 -
 ジアミン、及びメチル ピラジン - 2 - イミデートを用いて、実施例 205 と
 同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
 表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=6.9\text{ Hz}$), 3.3
 10 8 (2H, q, $J=6.9\text{ Hz}$), 6.77 - 6.91 (2H, m), 7.1
 7 - 7.24 (1H, m), 7.51 (1H, s), 7.52 (1H, dd,
 $J=7.4, 4.3\text{ Hz}$), 7.74 (1H, s), 8.04 (1H, d, J
 $=7.4\text{ Hz}$), 8.41 (1H, d, $J=2.3\text{ Hz}$), 8.74 (1H,
 d, $J=4.3\text{ Hz}$), 8.80 (1H, dd, $J=2.3, 1.8\text{ Hz}$),
 15 9.51 (1H, d, $J=1.8\text{ Hz}$)

ESI-MS (m/e): 510 $[\text{M}+\text{H}]$

実施例 235

5 - (2, 6 - ジフルオロ - フェノキシ) - 2 - ピリジン - 2 - イル - 6 -
 20 (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベンズイミダ
ゾール

実施例 221 (工程 2) で得られた 5 - フルオロ - 4 - (6 - エタンスルホ
 ニル - ピリジン - 3 - イルオキシ) - 2 - ニトロ - フェニルアミン、及び 2,
 6 - ジフルオロ - フェノールを用いて、実施例 221 (工程 3) と同様の方法、
 25 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
 を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.29 (3H, t, $J=7.4\text{ Hz}$), 3.3
 8 (1H, q, $J=7.4\text{ Hz}$), 3.39 (1H, q, $J=7.4\text{ Hz}$),
 6.68 - 6.75 (1/2H, m), 6.90 - 7.00 (2H, m), 7.

1 2-7. 26 (1H, m), 7. 27-7. 53 (3H, m), 7. 68-
 7. 72 (1/2H, m), 7. 84-7. 92 (1H, m), 7. 98-8.
 04 (1H, m), 8. 31-8. 39 (1H, m), 8. 41 (1/2H,
 d, J=2. 3Hz), 8. 56 (1/2H, d, J=2. 3Hz), 8. 5
 5 7-8. 63 (1H, m), 10. 59-10. 88 (1H, m)
 ESI-MS (m/e) : 509 [M+H]

実施例 236

5 - (2, 6-ジフルオロフェノキシ) - 2-ピラジン-2-イル-6-
 10 (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダ
 ゴール

実施例 235 で得られた 4 - (2, 6-ジフルオロフェノキシ) - 5 -
 (6-エタンスルホニル-ピリジン-3-イルオキシ) - ベンゼン-1, 2-
 ジアミン、及びピラジン-2-カルボン酸を用いて、実施例 197 と同様の方
 15 法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化
 合物を無色固体として得た。

¹HNMR (CDCl₃) δ : 1. 29 (3H, t, J=7. 4Hz), 3. 3
 8 (1/2H, q, J=7. 4Hz), 3. 39 (1H, q, J=7. 4H
 z), 3. 40 (1/2H, q, J=7. 4Hz), 6. 73-6. 78 (1
 20 /2H, m), 6. 93-7. 04 (2H, m), 6. 93-7. 04 (1/
 2H, m), 7. 14-7. 20 (1/2H, m), 7. 22 (1/4H,
 s), 7. 31-7. 42 (1H, m), 7. 44 (1/4H, s), 7. 4
 5 (1/4H, s), 7. 53 (1/4H, s), 7. 74 (1/4H, s),
 7. 75 (1/4H, s), 8. 00-8. 05 (1H, m), 8. 43 (1
 25 /2H, d, J=2. 7Hz), 8. 56 (1/4H, dd, J=2. 5, 1.
 6Hz), 8. 57 (1/2H, d, J=2. 7Hz), 8. 59 (1/4H,
 dd, J=2. 5, 1. 6Hz), 8. 60 (1/4H, dd, J=2. 5,
 1. 6Hz), 8. 61 (1/4H, dd, J=2. 5, 1. 6Hz), 8.
 66 (1/4H, d, J=2. 5Hz), 8. 67 (1/4H, d, J=2.

5 Hz), 8.68 (1/4H, d, J=2.5 Hz), 8.69 (1/4H, d, J=2.5 Hz), 9.56 (1/4H, d, J=1.6 Hz), 9.60 (1/4H, d, J=1.6 Hz), 9.61 (1/4H, d, J=1.6 Hz), 9.63 (1/4H, d, J=1.6 Hz), 10.36 (1/4H, brs), 10.48 (1/4H, brs), 10.51 (1/4H, brs), 10.57 (1/4H, brs)

ESI-MS (m/e) : 510 [M+H]

実施例 237

10 5-(2,6-ジフルオロフェノキシ)-2-(1-メチル-1H-ピラゾール-3-イル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 235 で得られた 4-(2,6-ジフルオロフェノキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及び 1-メチル-1H-ピラゾール-3-カルボン酸を用いて、実施例 203 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

¹H NMR (CDCl₃) δ : 1.29 (3H, t, J=7.4 Hz), 3.38 (2H, q, J=7.4 Hz), 3.96 (3H, s), 6.87 (1/2 H, brs), 6.93-7.00 (3H, m), 7.10-7.17 (1H, m), 7.18 (1/2 H, s), 7.30 (1/2 H, s), 7.32-7.40 (1H, m), 7.34 (1H, d, J=2.5 Hz), 7.63 (1/2 H, brs), 7.98-8.03 (1H, m), 8.54 (1H, d, J=2.7 Hz), 10.18 (1/2 H, brs), 10.35 (1/2 H, brs)

ESI-MS (m/e) : 512 [M+H]

実施例 238

5- (2-トリフルオロメトキシ-フェノキシ) -2-ピラジン-2-イル-
6- (6-エタンスルホニル-ピリジン-3-イルオキシ) -1H-ベンズイ
ミダゾール

実施例 221 (工程 2) で得られた 5-フルオロ-4- (6-エタンスルホ
5 ニル-ピリジン-3-イルオキシ) -2-ニトロ-フェニルアミン、及び 2-
トリフルオロメトキシ-フェノールを用いて、実施例 196 (工程 4)、(工
程 5)、及び実施例 205 と同様の方法、これに準じた方法又はこれらと常法
とを順次組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.27 (3H, t, $J=7.4\text{ Hz}$), 3.3
10 6 and 3.37 (total 2H, each q, $J=7.4\text{ Hz}$),
6.95-7.00 (1H, m), 7.12-7.46 (5H, m), 7.5
0 and 7.76 (total 1H, each s), 7.98 an
d 8.00 (total 1H, each d, $J=8.8\text{ Hz}$), 8.4
1 (1H, d, $J=2.7\text{ Hz}$), 8.59-8.62 (1H, m), 8.6
15 8 (1H, d, $J=2.4\text{ Hz}$), 9.61 and 9.63 (total
1H, each d, $J=1.6\text{ Hz}$)

ESI-MS (m/e): 558 $[\text{M}+\text{H}]$

実施例 239

20 5- (2-フルオロピリジン-3-イルオキシ) -6- (6-エタンスルホニ
ルピリジン-3-イルオキシ) -2-ピリジン-2-イル-1H-ベンズイミ
ダゾール

実施例 221 (工程 2) で得られた 5-フルオロ-4- (6-エタンスルホ
ニル-ピリジン-3-イルオキシ) -2-ニトロ-フェニルアミン、及び 2-
25 フルオロ-ピリジン-3-イルオキシ-2-イル-1H-ベンズイミダゾールを用いて、実施例 221 (工程 3) と同様の
方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.29 (3H, t, $J=7.4\text{ Hz}$), 3.3
8 (2H, q, $J=7.4\text{ Hz}$), 7.11-7.16 (1H, m), 7.2

4 (1/2H, s), 7.26-7.35 (2H, m), 7.41-7.45 (1H, m), 7.43 (1/2H, s), 7.55 (1/2H, s), 7.72 (1/2H, s), 7.88-7.94 (2H, m), 7.99-8.03 (1H, m), 8.38-8.41 (2H, m), 8.65-8.67 (1H, m), 10.94 (1/2H, brs), 10.98 (1/2H, brs)

ESI-MS (m/e) : 492 [M+H]

実施例240

10 5-(2-フルオロピリジン-3-イルオキシ)-6-(6-エタンスルホンルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例239で得られた4-(2-フルオロピリジン-3-イルオキシ)-5-(6-エタンスルホンルピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及びピラジン-2-カルボン酸を用いて、実施例197と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

¹HNMR (CDCl₃) δ : 1.30 (3H, t, J=7.4Hz), 3.38 (1H, q, J=7.4Hz), 3.39 (1H, q, J=7.4Hz), 7.13-7.24 (1H, m), 7.24 (1/2H, s), 7.26-7.39 (2H, m), 7.47 (1/2H, s), 7.56 (1/2H, s), 7.77 (1/2H, s), 7.95-8.05 (2H, m), 8.40 (1H, d, J=2.3Hz), 7.62 (1/2H, dd, J=2.4, 1.6Hz), 8.63 (1/2H, dd, J=2.4, 1.6Hz), 8.70 (1/2H, d, J=2.4Hz), 8.71 (1/2H, d, J=2.4Hz), 9.62 (1/2H, d, J=1.6Hz), 9.63 (1/2H, d, J=1.6Hz), 10.45 (1/2H, brs), 10.51 (1/2H, brs)

ESI-MS (m/e) : 493 [M+H]

実施例 2 4 1

5 5 - (2 - フルオロピリジン - 3 - イルオキシ) - 2 - (1 H - ピラゾール - 3 - イル) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 1 H - ベンズイミダゾール

実施例 2 3 9 で得られた 4 - (2 - フルオロピリジン - 3 - イルオキシ) - 5 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - ベンゼン - 1, 2 - ジアミン、及び 1 H - ピラゾール - 3 - カルボキサアルデヒドを用いて、実施例 2 0 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1. 2 9 (3H, t, $J=7.4\text{ Hz}$), 3. 3 7 (2H, q, $J=7.4\text{ Hz}$), 7. 0 7 (1H, d, $J=2.7\text{ Hz}$), 7. 0 8 - 7. 1 3 (1H, m), 7. 2 0 (1/2H, brs), 7. 2 4 - 7. 3 0 (2H, m), 7. 3 4 (1/2H, brs), 7. 5 2 (1/2H, brs), 7. 6 5 (1/2H, brs), 7. 7 1 (1H, d, $J=2.7\text{ Hz}$), 7. 8 8 - 7. 9 2 (1H, m), 7. 9 9 (1H, d, $J=8.6\text{ Hz}$), 8. 3 3 (1H, d, $J=2.7\text{ Hz}$)

ESI-MS (m/e): 481 [M+H]

20 実施例 2 4 2

5 - (2 - クロロピリジン - 3 - イルオキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール

実施例 2 2 1 (工程 2) で得られた 5 - フルオロ - 4 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ニトロフェニルアミン、及び 2 - クロロ - ピリジン - 3 - オールを用いて、実施例 2 2 1 (工程 3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

- ^1H NMR (CDCl_3) δ : 1.29 (3H, t, $J=7.4\text{ Hz}$), 3.38 (2H, q, $J=7.4\text{ Hz}$), 7.14–7.20 (2H, m), 7.28 (1/2H, s), 7.20–7.31 (1H, m), 7.40–7.46 (1H, m), 7.46 (1/2H, s), 7.60 (1/2H, s), 7.76 (1/2H, s), 7.88–7.93 (1H, m), 8.00 (1/2H, d, $J=8.6\text{ Hz}$), 8.01 (1/2H, d, $J=8.6\text{ Hz}$), 8.11–8.16 (1H, m), 8.31–8.35 (1H, m), 8.38–8.42 (1H, m), 8.64–8.68 (1H, m), 10.82–10.95 (1H, m)
- 10 ESI-MS (m/e): 508 $[\text{M}+\text{H}]$

実施例 243

- 5-(2-クロロピリジン-3-イルオキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール
- 15 ゾール

- 実施例 242 で得られた 4-(2-クロロピリジン-3-イルオキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及びピラジン-2-カルボン酸を用いて、実施例 197 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表
- 20 題化合物を無色固体として得た。

- ^1H NMR (CDCl_3) δ : 1.29 (3H, t, $J=7.4\text{ Hz}$), 3.37 (2H, q, $J=7.4\text{ Hz}$), 7.18–7.24 (2H, m), 7.30 (1/2H, s), 7.31 (1/2H, dd, $J=8.6, 2.7\text{ Hz}$), 7.32 (1/2H, dd, $J=8.6, 2.7\text{ Hz}$), 7.51 (1/2H, s), 7.61 (1/2H, s), 7.81 (1/2H, s), 8.02 (1/2H, d, $J=8.6\text{ Hz}$), 8.04 (1/2H, d, $J=8.6\text{ Hz}$), 8.15–8.20 (1H, m), 8.35 (1/2H, d, $J=2.7\text{ Hz}$), 8.36 (1/2H, d, $J=2.7\text{ Hz}$), 8.63 (1/2H, d, $J=2.3, 1.6\text{ Hz}$), 8.64 (1/2H, dd, $J=2.3, 1.$
- 25

6 Hz), 8.72 (1/2H, d, J=2.3 Hz), 8.73 (1/2H, d, J=2.3 Hz), 9.64 (1/2H, d, J=1.6 Hz), 9.65 (1/2H, d, J=1.6 Hz), 10.60 (1/2H, brs), 10.68 (1/2H, brs)

5 ESI-MS (m/e) : 509 [M+H]

実施例 244

5-(2-クロロピリジン-3-イルオキシ)-2-(1-メチル-1H-ピラゾール-3-イル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 242 で得られた 4-(2-クロロピリジン-3-イルオキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及び 1-メチル-1H-ピラゾール-3-カルボン酸を用いて、実施例 203 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

¹HNMR (CDCl₃) δ : 1.29 (3H, t, J=7.4 Hz), 3.37 (2H, q, J=7.4 Hz), 4.01 (3H, s), 7.01 (1H, d, J=2.3 Hz), 7.12-7.17 (2H, m), 7.26 (1H, dd, J=8.8, 2.7 Hz), 7.39 (1/2H, brs), 7.48 (1/2H, brs), 7.49 (1H, d, J=2.3 Hz), 7.58 (1/2H, brs), 7.69 (1/2H, brs), 7.99 (1H, d, J=8.8 Hz), 8.10-8.15 (1H, m), 8.31 (1H, d, J=2.7 Hz), 10.28 (1H, brs)

ESI-MS (m/e) : 511 [M+H]

25

実施例 245

5-(2-シアノピリジン-3-イルオキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 2 2 1 (工程 2) で得られた 5-フルオロ-4-(6-エタンスルホ
ニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニルアミン、及び 1-
オキシ-ピリジン-3-オールを用いて、実施例 2 1 8 と同様の方法、これに
準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色
5 固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1. 3 0 (3H, t, $J=7.4\text{ Hz}$), 3. 3
7 (2H, q, $J=7.4\text{ Hz}$), 7. 1 2-7. 2 6 (3H, m), 7. 3
8-7. 4 5 (2H, m), 7. 4 5 (1/2H, s), 7. 4 6 (1/2H,
s), 7. 7 5 (1H, s), 7. 8 9-7. 9 4 (1H, m), 7. 9 9-
10 8. 0 5 (1H, m), 8. 2 2-8. 2 6 (1H, m), 8. 3 9-8. 4
3 (1H, m), 8. 6 7-8. 7 0 (1H, m), 10. 8 8 (1H, br
s)

ESI-MS (m/e): 499 $[\text{M}+\text{H}]$

15 実施例 2 4 6

5-(2-シアノピリジン-3-イルオキシ)-6-(6-エタンスルホニル
ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダ
ゾール

実施例 2 4 5 で得られた 4-(2-シアノピリジン-3-イルオキシ)-
20 5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,
2-ジアミン、及びピラジン-2-カルボン酸を用いて、実施例 1 9 7 と同様
の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表
題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1. 3 5 (3/2H, t, $J=7.4\text{ Hz}$), 1.
25 3 7 (3/2H, t, $J=7.4\text{ Hz}$), 3. 3 8 (1H, q, $J=7.4\text{ Hz}$)
z), 3. 3 9 (1H, q, $J=7.4\text{ Hz}$), 7. 1 9-7. 2 6 (2H,
m), 7. 4 2-7. 4 7 (1H, m), 7. 5 3 (1/2H, s), 7. 5
4 (1/2H, s), 7. 8 0 (1/2H, s), 7. 8 1 (1/2H, s),
8. 0 4 (1/2H, d, $J=8.6\text{ Hz}$), 8. 0 5 (1/2H, d, $J=$

8. 6 Hz), 8. 22-8. 25 (1H, m), 8. 40-8. 43 (1H, m), 8. 64-8. 66 (1H, m), 8. 73 (1H, d, J=2. 5 Hz), 9. 65 (1H, d, J=1. 5 Hz), 10. 87 (1/2H, br s), 10. 90 (1/2H, br s)

5 ESI-MS (m/e) : 500 [M-H]

実施例 247

5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(6-エ
タンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1

10 H-ベンズイミダゾール

実施例 221 (工程 2) で得られた 5-フルオロ-4-(6-エタンスルホ
ニル-ピリジン-3-イルオキシ)-2-ニトロフェニルアミン、及び 2-
ジフルオロメトキシ-ピリジン-3-オールを用いて、実施例 221 (工程
3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
15 により、表題化合物を無色固体として得た。

¹H NMR (DMSO-d₆) δ : 1. 10 (3H, t, J=7. 4 Hz), 3.
36 (2H, q, J=7. 4 Hz), 7. 18-7. 25 (1H, m), 7.
31-7. 87 (6H, m), 7. 94-8. 07 (3H, m), 8. 32-
8. 36 (1H, m), 8. 46-8. 49 (1H, m), 8. 77 (1H,
20 s)

ESI-MS (m/e) : 540 [M+H]

実施例 248

5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(6-エ
タンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1
25 H-ベンズイミダゾール

実施例 247 で得られた 4-(2-ジフルオロメトキシ-ピリジン-3-イ
ルオキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベ
ンゼン-1, 2-ジアミン、及びメチル ピラジン-2-イミデートを用いて、

実施例 205 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.30 (3H, t, $J=7.4\text{ Hz}$), 3.37 (2H, q, $J=7.4\text{ Hz}$), 7.07–7.11 (1H, m), 7.157 and 7.76 (total 1H, each s), 7.29–7.34 (2H, m), 7.37 (1H, t, $J=72.8\text{ Hz}$), 7.46 (1H, s), 7.96–8.03 (2H, m), 8.43 (1H, s), 8.60 and 8.62 (total 1H, each s), 8.69 (1H, s), 9.60 and 9.63 (total 1H, each d, $J=1.5\text{ Hz}$)

ESI-MS (m/e): 541 $[\text{M}+\text{H}]$

実施例 249

5 – (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) – 6 – (6-エ
15 タンスルホニル-ピリジン-3-イルオキシ) – 2 – (1-メチル-1H-ピ
ラゾール-3-イル) – 1H-ベンズイミダゾール

実施例 247 で得られた 4 – (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) – 5 – (6-エタンスルホニル-ピリジン-3-イルオキシ) – ベンゼン-1, 2-ジアミン、及び 1-メチル-1H-ピラゾール-3-カルボン酸を用いて、実施例 203 と同様の方法、これに準じた方法又はこれらと常
20 法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ : 1.10 (3H, t, $J=7.4\text{ Hz}$), 3.36 (2H, q, $J=7.4\text{ Hz}$), 4.00 (3H, s), 6.88 (1H, d, $J=2.3\text{ Hz}$), 7.19 (1H, brs), 7.26–7.75 (4
25 H, m), 7.63 (1H, t, $J=72.4\text{ Hz}$), 7.90–7.99 (3H, m), 8.45 (1H, d, $J=2.7\text{ Hz}$)

ESI-MS (m/e): 543 $[\text{M}+\text{H}]$

実施例 250

6-ベンジルオキシ-5-(2-フルオロフェノキシ)-2-ピラジン-2-
イル-1H-ベンズイミダゾール

(工程1)

4-ベンジルオキシ-3-フルオロアニリンの合成

- 5 4-ベンジルオキシ-3-フルオロニトロベンゼン 4.94 g のメタノール
60 ml 溶液に、ヒドラジン-水和物 2.91 ml 及び展開ラネーニッケル触
媒約 1 g を加え、反応液を室温で 2 時間攪拌した。触媒をセライトにより濾去
後、溶媒を減圧留去することにより、表題化合物を黄色油状物質として得た。

(工程2)

- 10 N-(4-ベンジルオキシ-3-フルオロフェニル)ピラジンカルボキサミ
ドの合成

- 4-ベンジルオキシ-3-フルオロアニリン 4.13 g のピリジン 60 ml
溶液に、ピラジン-2-カルボン酸 2.59 g 及び 1-(3-ジメチルアミノ
プロピル)-3-エチルカルボジイミド・一塩酸塩 4.73 g を加え、反応液
15 を室温にて終夜攪拌した。ピリジンを減圧留去した後、水を加えた。生成した
沈殿物を濾取することにより、表題化合物を褐色固体として得た。

(工程3)

N-(4-ベンジルオキシ-5-フルオロ-2-ニトロフェニル)ピラジン
カルボキサミドの合成

- 20 N-(4-ベンジルオキシ-3-フルオロフェニル)ピラジンカルボキサミ
ド 5.80 g のクロロホルム 40 ml 懸濁液に、氷冷下、トリフルオロ酢酸 4
0 ml 及び硝酸カリウム 1.99 g を加え、反応液を室温にて終夜攪拌した。
溶媒を減圧留去した後、飽和重曹水を加えた。生成した沈殿物を濾取した後に、
水にて洗浄した。得られた固体を酢酸エチル及びヘキサンの混合溶媒にて洗浄
25 することにより、表題化合物を黄色固体として得た。

(工程4)

N-(4-ベンジルオキシ-5-(2-フルオロフェノキシ)-2-ニトロ
フェニル)ピラジンカルボキサミドの合成

N-(4-ベンジルオキシ-5-フルオロ-2-ニトロフェニル)ピラジンカルボキサミド 2.14 g のジメチルホルムアミド 16 ml 溶液に、2-フルオロフェノール 0.54 ml 及び炭酸カリウム 2.53 g を加え、反応液を 90 度で 5 時間攪拌した後、水を加えた。生成した沈殿物を濾取することにより、
5 表題化合物を黄色固体として得た。

(工程 5)

5-ベンジルオキシ-6-(2-フルオロフェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾールの製造

N-(4-ベンジルオキシ-5-(2-フルオロフェノキシ)-2-ニトロ
10 フェニル)ピラジンカルボキサミド 1.52 g のジメチルホルムアミド 16 ml 懸濁液に、塩化スズ (II) 二水和物 3.72 g を加え、反応液を 80 度にて終夜攪拌した。反応液を酢酸エチルにて希釈し、飽和重曹水、水及び飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、
15 得られた残渣を酢酸エチル及びヘキサンの混合溶媒にて洗浄することにより、
表題化合物を黄色固体として得た。

^1H NMR (DMSO- d_6) δ : 5.15 and 5.17 (total 2H, each s), 6.78-6.93 (1H, m), 7.06-7.40 (9H, m), 7.54 and 7.57 (total 1H, each s), 8.73 and 8.74 (total 1H, each s), 8.
20 76-8.79 (1H, m), 9.43 and 9.44 (total 1H, each d, $J=1.6\text{ Hz}$)

ESI-MS (m/e): 413 [M+H]

実施例 251

25 5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(2-シアノ-ピリミジン-5-イルオキシ)-1H-ベンズイミダゾール

(工程 1)

5-(2-フルオロフェノキシ)-6-ヒドロキシ-2-ピラジン-2-イル-1H-ベンズイミダゾールの合成

実施例 250 で得られた 5-(2-フルオロフェノキシ)-6-(2-フルオロフェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール 697 mg のメタノール 10 ml 及びテトラヒドロフラン 10 ml 懸濁液に、20%水酸化パラジウム-炭素触媒 500 mg を加え、反応液を水素雰囲気下室温にて 1 時間攪拌した。触媒をセライトにより濾去後、溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：酢酸エチル）にて精製し、表題化合物を黄色固体として得た。

（工程 2）

10 5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(2-シアノーピリミジン-5-イルオキシ)-1H-ベンズイミダゾールの製造

工程 1 で得られた 5-(2-フルオロフェノキシ)-6-ヒドロキシ-2-ピラジン-2-イル-1H-ベンズイミダゾール 7.0 mg の N-メチルピロリジノン 0.5 ml 溶液に、5-ブロモ-2-シアノーピリミジン 7.0 mg、炭酸セシウム 15 mg を加えた後、反応液を 90 度にて 15 分間攪拌した。反応混合物を、逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相：水-アセトニトリル-0.1%トリフルオロ酢酸] にて精製した。得られたフラクションを酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去することにより、表題化合物を無色固体として得た。

20 $^1\text{H-NMR}$ (CD_3OD) δ : 7.01-7.58 (5H, m), 7.64-7.82 (1H, m), 8.52 (2H, s), 8.67 (1H, s), 8.74 (1H, s), 9.44 (1H, s)

ESI-MS (m/e): 426 [M+H]

25 実施例 252

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-シアノーピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 251 (工程 1) で得られた 5-(2-フルオロフェノキシ)-6-ヒドロキシ-2-ピラジン-2-イル-1H-ベンズイミダゾール、及び 5-ブ

ロモ-2-シアノピリジンを用いて、実施例251(工程2)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 7.01–7.30 (5H, m), 7.42 (1H, dd, $J=8.6, 3.1\text{ Hz}$), 7.55–7.77 (1H, m), 7.81 (1H, d, $J=8.6\text{ Hz}$), 8.39 (1H, d, $J=3.1\text{ Hz}$), 8.71 (1H, s), 8.77 (1H, s), 9.47 (1H, s)

ESI-MS (m/e): 425 $[\text{M}+\text{H}]$

10 実施例253

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-トリフルオロメチル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例251(工程1)で得られた5-(2-フルオロフェノキシ)-6-ヒドロキシ-2-ピラジン-2-イル-1H-ベンズイミダゾール21mgのN-メチルピロリジノン1ml溶液に、5-ブロモ-2-トリフルオロメチル-ピリジン16mg、炭酸セシウム50mg、及び酸化銅(II)10mgを加えた後、反応液を130度にて5時間攪拌した。沈殿物を濾別した後、溶液を逆相中圧液体クロマトグラフィー[ODS-AS-360-CC(YMC社製)移動相:水-アセトニトリル-0.1%トリフルオロ酢酸]にて精製した。得られたフラクションを酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去することにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 6.70–7.84 (6H, m), 7.49 (1H, dd, $J=8.8\text{ Hz}, 2.8\text{ Hz}$), 7.78 (1H, d, $J=8.8\text{ Hz}$), 8.39 (1H, d, $J=2.8\text{ Hz}$), 8.73 (1H, s), 8.80 (1H, s), 9.49 (1H, s)

ESI-MS (m/e): 468 $[\text{M}+\text{H}]$

実施例254

5 - (2, 6-ジフルオロ-フェノキシ) - 4-フルオロ-2-ピラジン-
2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1
H-ベンズイミダゾール

(工程 1)

- 5 2, 3-ジフルオロ-1-(6-メタンスルホニル-ピリジン-3-イルオキシ) - 4-ニトロ-ベンゼンの合成

2, 3, 4-トリフルオロ-ニトロベンゼン 135 mg の N-メチルピロリジノン 3 ml 溶液に、6-メタンスルホニル-ピリジン-3-オール 112 mg、及び炭酸カリウム 100 mg を加え、反応液を 50 度にて 1 時間攪拌した。

- 10 反応液を酢酸エチルにて希釈し、水及び飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／1）にて精製し、表題化合物を得た。

(工程 2)

- 15 N-(2, 3-ジフルオロ-4-(6-メタンスルホニル-ピリジン-3-イルオキシ) - 6-ニトロ-フェニル) ピラジンカルボキサミドの合成

2, 3-ジフルオロ-1-(6-メタンスルホニル-ピリジン-3-イルオキシ) - 4-ニトロ-ベンゼン 22 mg のメタノール 3 ml 溶液に、ヒドラジン-水和物 0.2 ml 及び展開ラネーニッケル触媒約 0.01 g を加え、反応液を室温で 15 分間攪拌した。触媒をセライトにより濾去後、溶媒を減圧留去することにより、粗生成物を得た。得られた粗生成物のピリジン 1 ml 溶液に、ピラジン-2-カルボン酸 12 mg 及び 1-(3-ジメチルアミノプロピル) - 3-エチルカルボジイミド・一塩酸塩 25 mg を加え、反応液を室温にて終夜攪拌した。反応液を酢酸エチルにて希釈し、水及び飽和食塩水にて順次

- 25 洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、粗生成物を得た。粗生成物のトリフルオロ酢酸 2 ml 溶液に、発煙硝酸 0.1 ml を加え、反応液を 45 度にて一終夜攪拌した。溶媒を減圧留去した後、得られた残渣を分取用薄層クロマトグラフィー（Kieselgel TM 60 F 254、Art 5

744 (メルク社製)、クロロホルム/メタノール=20/1)にて精製し、表題化合物を得た。

(工程3)

5 5- (2, 6-ジフルオロフェノキシ) -4-フルオロ-2-ピラジン-2-イル-6- (6-メタンスルホニル-ピリジン-3-イルオキシ) -1H-ベンズイミダゾールの製造

N- (2, 3-ジフルオロ-4- (6-メタンスルホニル-ピリジン-3-イルオキシ) -6-ニトロフェニル) ピラジンカルボキサミド 8.6 mg の N-メチルピロリジノン 0.5 ml 溶液に、2, 6-ジフルオロフェノール 8 mg 及び炭酸カリウム 8 mg を加え、反応液を 90 度で 15 分間攪拌した後、塩化スズ (II) 二水和物 75 mg を加え、反応液を 90 度にて一終夜攪拌した。さらに p-トルエンスルホン酸 3 mg を加え、反応液を 90 度で 2 時間攪拌した。沈殿物を濾別した後、溶液を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.22 (3H, s), 6.93-6.99 (2H, m), 7.01-7.10 (1H, m), 7.30-7.45 (1H, m), 7.47-7.51 (1H, m), 8.02 (1H, d, $J=8.6$ Hz), 8.37 (1H, d, $J=2.3$ Hz), 8.75 (1H, d, $J=2.3$ Hz), 8.80 (1H, s), 9.56 (1H, s)

ESI-MS (m/e): 514 $[\text{M}+\text{H}]$

25 実施例 255

5- (2, 6-ジフルオロフェノキシ) -7-フルオロ-2-ピリジン-2-イル-6- (6-エタンスルホニル-ピリジン-3-イルオキシ) -1H-ベンズイミダゾール

(工程1)

2, 3-ジフルオロ-1-(2, 6-ジフルオロフェノキシ)-4-ニトロベンゼンの合成

2, 3, 4-トリフルオロニトロベンゼン 500 mg の N-メチルピロリジノン 13 ml 溶液に、2, 6-ジフルオロフェノール 470 mg、及びテ
 5 トラブチルアンモニウムブロミド 1.5 g を加え、反応液を 130 度にて一終夜攪拌した。反応液を酢酸エチルにて希釈し、水及び飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝4／1）にて精製し、表題化合物を得た。

10 (工程 2)

5-(2, 6-ジフルオロフェノキシ)-7-フルオロ-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

2, 3-ジフルオロ-1-(2, 6-ジフルオロフェノキシ)-4-ニ
 15 ロ-ベンゼン、及び参考例 4 で得られた 6-エタンスルホニル-ピリジン-3-オールを順次用いて、実施例 254（工程 2）、（工程 3）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 3.4
 20 1 (2H, q, $J=7.4\text{ Hz}$), 6.91-6.96 (1H, m), 7.14 (2H, t, $J=8.4\text{ Hz}$), 7.27-7.34 (1H, m), 7.48-7.54 (1H, m), 7.63 (1H, dd, $J=8.8, 2.7\text{ Hz}$), 7.99 (1H, t, $J=7.6\text{ Hz}$), 8.10 (1H, d, $J=8.8\text{ Hz}$), 8.31-8.37 (1H, m), 8.59 (1H, d, $J=2.7\text{ Hz}$), 8.70-8.76 (1H, m)

ESI-MS (m/e): 527 [$M+H$]

実施例 256

5 - (ピリジン-2-イルオキシ) - 2-ピリジン-2-イル-6 - (4-メ
タンスルホニル-フェノキシ) - 1H-ベンズイミダゾール

- 実施例14で得られた5-フルオロ-4-(4-メタンスルホニル-フェノ
キシ) - 2-ニトロ-フェニルアミン、及び2-ヒドロキシピリジンを用いて、
5 実施例14と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ
ることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.09 (3H, s), 6.81 (1H, d, J
= 8.2 Hz), 7.02 (2H, d, J = 8.6 Hz), 7.02-7.0
7 (1H, m), 7.49-7.54 (1H, m), 7.55 (1H, s),
10 7.63 (1H, s), 7.71-7.77 (1H, m), 7.83 (2H,
d, J = 8.6 Hz), 7.98-8.03 (2H, m), 8.31 (1H,
d, J = 7.6 Hz), 8.76 (1H, d, J = 4.3 Hz)

ESI-MS (m/e): 459 [M+H]

15 実施例257

5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (4-メ
タンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1H-ベンズイミ
ダゾール

- 実施例14で得られた5-フルオロ-4-(4-メタンスルホニル-フェノ
キシ) - 2-ニトロ-フェニルアミン、及び2-ジフルオロメトキシ-ピリジ
ン-3-オールを用いて、実施例14と同様の方法、これに準じた方法又はこ
れらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.10 (3H, s), 7.05 (2H, d, J
= 8.4 Hz), 7.13-7.20 (1H, m), 7.33-7.70 (4
25 H, m), 7.48 (1H, t, J = 7.2. 8 Hz), 7.87 (2H, d,
 J = 8.4 Hz), 7.92 (1H, d, J = 4.5 Hz), 8.01 (1H,
t, J = 7.4 Hz), 8.32 (1H, d, J = 7.8 Hz), 8.77
(1H, b r s)

ESI-MS (m/e): 525 [M+H]

実施例 258

5 5-(1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 14 で得られた 5-フルオロ-4-(4-メタンスルホニル-フェノキシ)-2-ニトロ-フェニルアミン、及び 1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-オールを用いて、実施例 14 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を
10 褐色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.04 (3H, s), 3.56 (3H, s), 6.06 (1H, td, $J=7.0, 2.7\text{ Hz}$), 6.84 (1/2H, d, $J=7.4\text{ Hz}$), 6.88 (1/2H, dd, $J=7.4, 1.8\text{ Hz}$), 7.05-7.15 (3H, m), 7.20 (1/2H, s), 7.28 (1/2H, d, $J=1.2\text{ Hz}$), 7.38 (1H, dd, $J=6.6, 4.7\text{ Hz}$), 7.46 (1/2H, s), 7.60 (1/2H, s), 7.80-7.90 (3H, m), 8.36 (1H, t, $J=7.2\text{ Hz}$), 8.62 (1H, d, $J=4.4\text{ Hz}$)

ESI-MS (m/e): 489 $[\text{M}+\text{H}]$

20

実施例 259

5 5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(4-エタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール
25 (工程 1)

5-フルオロ-4-(4-エタンスルホニル-フェノキシ)-2-ニトロ-フェニルアミンの合成

6-エタンスルホニル-ピリジン-3-オールを用いて、実施例14と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

(工程2)

- 5 5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(4-エタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾールの製造

- 10 5-フルオロ-4-(4-エタンスルホニル-フェノキシ)-2-ニトロ-フェニルアミン、及び2-ジフルオロメトキシ-ピリジン-3-オールを用いて、実施例14と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- $^1\text{H NMR}$ (CD_3OD) δ : 1.20 (3H, t, $J=7.4\text{ Hz}$), 3.15 (2H, q, $J=7.4\text{ Hz}$), 7.04 (2H, d, $J=8.4\text{ Hz}$), 7.06-7.15 (1H, m), 7.30-7.70 (4H, m), 7.46 (1H, t, $J=72.9\text{ Hz}$), 7.80 (2H, d, $J=8.4\text{ Hz}$), 7.89 (1H, d, $J=4.3\text{ Hz}$), 7.99 (1H, t, $J=7.7\text{ Hz}$), 8.30 (1H, d, $J=8.0\text{ Hz}$), 8.74 (1H, brs)
ESI-MS (m/e): 539 [M+H]

20 実施例260

5-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(4-エタンスルホニル-フェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

- 25 実施例259(工程2)で得られた4-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-5-(4-エタンスルホニル-フェノキシ)-ベンゼン-1,2-ジアミンを用いて、実施例197と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.27 and 1.28 (total 3H, each t, $J=7.4\text{Hz}$), 3.09 and 3.10 (total 2H, each q, $J=7.4\text{Hz}$), 6.98 and 6.99 (total 2H, each d, $J=9.0\text{Hz}$), 7.04–7.10 (1H, m), 7.23 and 7.42 (total 1H, each s), 7.25–7.30 (1H, m), 7.36 and 7.37 (total 1H, each t, $J=73.0\text{Hz}$), 7.52 and 7.73 (total 1H, each s), 7.80 and 7.81 (total 2H, each d, $J=9.0\text{Hz}$), 7.90–7.96 (1H, m), 8.58–8.63 (1H, m), 8.68 and 8.69 (total 1H, each d, $J=2.4\text{Hz}$), 9.61 and 9.63 (total 1H, each d, $J=1.5\text{Hz}$)

ESI-MS (m/e): 540 $[\text{M}+\text{H}]$

15 実施例261

5-(2,4-ジフルオロフェノキシ)-6-(4-エタンスルホニルフェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例259(工程1)で得られた4-フルオロ-5-(4-エタンスルホニルフェノキシ)-2-ニトロフェニルアミン、及び2,4-ジフルオロフェノールを用いて、実施例259と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

^1H NMR (CD_3OD) δ : 1.21 (3H, t, $J=7.4\text{Hz}$), 3.19 (2H, q, $J=7.4\text{Hz}$), 6.89–6.95 (1H, m), 7.01–7.12 (2H, m), 7.11 (2H, d, $J=8.4\text{Hz}$), 7.23–7.67 (3H, m), 7.84 (2H, d, $J=8.4\text{Hz}$), 7.99 (1H, t, $J=7.4\text{Hz}$), 8.29 (1H, d, $J=8.2\text{Hz}$), 8.75 (1H, brs)

ESI-MS (m/e): 508 $[\text{M}+\text{H}]$

実施例 262

4-(1-メチル-1H-イミダゾール-2-イルスルファニル)-6-(4-ジメチルカルバモイル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 5 1-メチル-1H-イミダゾール-2-チオール及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡褐色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.09 (6H, s), 3.87 (3H, s),
10 6.69 (1H, s), 6.74 (1H, s), 6.79-6.89 (2H, m), 7.07 (2H, d, $J=8.4\text{ Hz}$), 7.16 (1H, d, $J=2.0\text{ Hz}$), 7.42 (2H, d, $J=8.4\text{ Hz}$), 7.53 (1H, t, $J=7.6\text{ Hz}$), 7.64 (1H, d, $J=2.0\text{ Hz}$), 8.17 (1H, d, $J=7.4\text{ Hz}$)

15 ESI-MS (m/e): 471 $[\text{M}+\text{H}]$

実施例 263

4-(ピリジン-2-イルスルファニル)-6-(4-ジメチルカルバモイル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 20 ピリジン-2-チオール及び4-ヒドロキシ-N, N-ジメチルベンズアミドを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡褐色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.05 (3H, s), 3.09 (3H, s),
6.90-7.08 (4H, m), 7.30-7.65 (6H, m), 7.8
25 5 (1H, t, $J=7.5\text{ Hz}$), 8.37 (1H, d, $J=7.8\text{ Hz}$),
8.45 (1H, d, $J=3.9\text{ Hz}$), 8.62 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 468 $[\text{M}+\text{H}]$

実施例 264

4-(2,6-ジフルオロフェノキシ)-6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2,6-ジフルオロフェノール、及び4-メタンスルホニルフェノール
5 を順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.22 (3H, s), 6.25 (1H, s),
7.16-7.24 (3H, m), 7.49-7.54 (1H, m), 7.60-7.66 (1H, m), 7.70-7.78 (1H, m), 7.95 (2
10 H, d, $J=8.4\text{ Hz}$), 8.02 (1H, m), 8.40 (1H, d, $J=4.7\text{ Hz}$), 8.70 (1H, d, $J=2.3\text{ Hz}$), 8.78 (1H, d, $J=2.3\text{ Hz}$)

ESI-MS (m/e): 494 [M+H]

15 実施例 265

4-(1-メチル-2-オキソ-1,2-ジヒドロピリジン-3-イルオキシ)-6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

3-ヒドロキシ-1-メチル-1H-ピリジン-2-オン、及び4-メタン
20 スルホニルフェノールを順次用いて、実施例67と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.10 (3H, s), 3.63 (3H, s),
6.35 (1H, t, $J=7.1\text{ Hz}$), 6.39 (1H, s), 7.06
25 (1H, s), 7.16 (2H, d, $J=8.0\text{ Hz}$), 7.34 (1H, d, $J=7.2\text{ Hz}$), 7.42-7.52 (1H, m), 7.53 (1H, dd, $J=6.8, 1.6\text{ Hz}$), 7.90 (2H, d, $J=8.0\text{ Hz}$), 7.91-8.00 (1H, m), 8.28-8.38 (1H, m), 8.71 (1H, s)

ESI-MS (m/e) : 489 [M+H]

実施例 266

4- (2, 6-ジフルオロフェノキシ) -6- (6-メタンスルホニル-ピ
5 リジン-3-イルオキシ) -2-ピラジン-2-イル-1H-ベンズイミダ
ゾール

2, 6-ジフルオロフェノール、及び参考例 3 で得られた 6-メタンスル
ホニル-ピリジン-3-オールを順次用いて、実施例 68 と同様の方法、これ
に準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得
10 た。

¹HNMR (CD₃OD) δ : 3.22 (3H, s), 6.39 (1H, s),
7.16-7.24 (2H, m), 7.21 (1H, d, J=8.6 Hz),
7.32-7.40 (1H, m), 7.54-7.58 (1H, m), 8.0
6 (1H, d, J=8.6 Hz), 8.47 (1H, d, J=2.3 Hz),
15 8.72 (1H, d, J=2.3 Hz), 8.79 (1H, s), 9.56
(1H, s)

ESI-MS (m/e) : 496 [M+H]

実施例 267

20 4- (2, 6-ジフルオロフェノキシ) -6- (6-メタンスルホニル-ピ
リジン-3-イルオキシ) -2-ピリジン-2-イル-1H-ベンズイミダ
ゾール

実施例 266 で得られた 3- (2, 6-ジフルオロフェノキシ) -5-
(6-メタンスルホニル-ピリジン-3-イルオキシ) -ベンゼン-1, 2-
25 ジアミンを用いて、実施例 196 (工程 6) と同様の方法、これに準じた方法
又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CD₃OD) δ : 3.32 (3H, s), 6.47 (1H, s),
7.19-7.26 (3H, m), 7.34-7.42 (1H, m), 7.5
6-7.63 (2H, m), 8.05-8.11 (2H, m), 8.41 (1

H, d, $J=8.6\text{ Hz}$), 8.48 (1H, d, $J=2.3\text{ Hz}$), 8.83 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 495 [M+H]

5 実施例 268

4-(2,6-ジフルオロフェノキシ)-6-(6-エタンスルホニルペリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

2,6-ジフルオロフェノール、及び参考例4で得られた6-エタンスルホニルペリジン-3-オールを順次用いて、実施例68と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 3.40 (2H, q, $J=7.4\text{ Hz}$), 6.38 (1H, s), 7.10-7.25 (3H, m), 7.32-7.40 (1H, m), 7.56 (1H, dd, $J=8.6, 2.3\text{ Hz}$), 8.06 (1H, d, $J=9.0\text{ Hz}$), 8.48 (1H, d, $J=2.7\text{ Hz}$), 8.72 (1H, d, $J=2.7\text{ Hz}$), 8.79 (1H, s), 9.56 (1H, s)

ESI-MS (m/e): 510 [M+H]

20

実施例 269

4-(2,6-ジフルオロフェノキシ)-6-(6-エタンスルホニルペリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

25 実施例268で得られた3-(2,6-ジフルオロフェノキシ)-5-(6-エタンスルホニルペリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンを用いて、実施例196(工程6)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.4

0 (2H, q, $J=7.4\text{ Hz}$), 6.44 (1H, s), 7.18–7.25 (3H, m), 7.32–7.41 (1H, m), 7.55–7.62 (2H, m), 8.03–8.09 (2H, m), 8.41 (1H, d, $J=7.8\text{ Hz}$), 8.49 (1H, d, $J=2.3\text{ Hz}$), 8.81 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 509 [M+H]

実施例 270

4-(2-フルオロ-ピリジン-3-イルオキシ)-6-(6-メタンスルホ
 10 ニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズ
 イミダゾール

2-フルオロ-ピリジン-3-オール、及び6-メタンスルホニル-ピリジン-3-オールを順次用いて、実施例68と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

15 $^1\text{H NMR}$ (DMSO- d_6) δ : 3.23 (3H, s), 6.09 (1H, d, $J=2.3\text{ Hz}$), 6.35 (1H, d, $J=2.3\text{ Hz}$), 7.28 (1H, dd, $J=7.8, 5.5\text{ Hz}$), 7.59–7.61 (1H, m), 7.66–7.67 (1H, m), 7.84–7.85 (1H, m), 8.06 (1H, d, $J=8.6\text{ Hz}$), 8.70–8.74 (1H, m), 8.87 (1
 20 H, d, $J=2.3\text{ Hz}$), 9.15 (1H, d, $J=1.6\text{ Hz}$), 9.86 (1H, s)

ESI-MS (m/e): 479 [M+H]

実施例 271、272

25 4-(2-フルオロ-ピリジン-3-イルオキシ)-6-(6-メタンスル
 ホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベン
 ズイミダゾール及び4-(2-オキソ-1,2-ジヒドロ-ピリジン-3-イ
 ルオキシ)-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-
 2-ピリジン-2-イル-1H-ベンズイミダゾール

2-フルオロ-ピリジン-3-オール、及び6-メタンスルホニル-ピリジン-3-オールを順次用いて、実施例108-1、108-2と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をそれぞれ得た。

5 4-(2-フルオロ-ピリジン-3-イルオキシ)-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

^1H NMR (CD_3OD) δ : 3.23 (3H, s), 6.19 (1H, d, $J=2.3\text{ Hz}$), 6.55 (1H, d, $J=2.3\text{ Hz}$), 7.23 (1H, dd, $J=4.2, 2.1\text{ Hz}$), 7.61-7.64 (2H, m), 7.67 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 7.84-7.85 (1H, m), 8.02 (1H, td, $J=7.8, 1.6\text{ Hz}$), 8.09 (1H, d, $J=8.6\text{ Hz}$), 8.16 (1H, d, $J=7.8\text{ Hz}$), 8.51 (1H, d, $J=2.3\text{ Hz}$), 8.68 (1H, d, $J=4.7\text{ Hz}$)
 15 ESI-MS (m/e): 478 $[\text{M}+\text{H}]$

6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-4-(2-オキソ-1,2-ジヒドロ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

20 ^1H NMR ($\text{DMSO}-d_6$) δ : 3.25 (3H, s), 6.61-6.62 (2H, m), 6.97-7.00 (2H, m), 7.63-7.67 (2H, m), 8.02-8.11 (4H, m), 8.56 (1H, d, $J=2.3\text{ Hz}$), 8.74 (1H, d, $J=4.7\text{ Hz}$), 10.33 (1H, s)
 ESI-MS (m/e): 476 $[\text{M}+\text{H}]$

25

実施例273

4-(2-フルオロ-ピリジン-3-イルオキシ)-6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-フルオロ-ピリジン-3-オール、及び4-メタンスルホニル-フェ

ノールを順次用いて、実施例 67 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 3.13 (3H, s), 6.67 (1H, d, $J=2.0\text{ Hz}$), 7.21–7.25 (2H, m), 7.35–7.39 (2
5 H, m), 7.60–7.63 (1H, m), 7.77–7.82 (1H, m), 7.95–7.97 (2H, m), 8.00–8.09 (2H, m), 8.36 (1H, d, $J=8.2\text{ Hz}$), 8.83 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 477 $[\text{M}+\text{H}]$

10

実施例 274

4-(1-メチル-2-オキソ-1,2-ジヒドロピリジン-3-イルオキシ)-6-(4-エタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

15 (工程 1)

5-(4-エタンスルホニル-フェノキシ)-3-(1-メチル-2-オキソ-1,2-ジヒドロピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンの合成

20 3-ヒドロキシ-1-メチル-1H-ピリジン-2-オン、及び 4-エタンスルホニル-フェノールを順次用いて、実施例 67 (工程 1) 乃至 (工程 4) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色油状物質として得た。

(工程 2)

25 4-(1-メチル-2-オキソ-1,2-ジヒドロピリジン-3-イルオキシ)-6-(4-エタンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾールの製造

(工程 1) で得られた 5-(4-エタンスルホニル-フェノキシ)-3-(1-メチル-2-オキソ-1,2-ジヒドロピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンを用いて、実施例 204 (工程 2) と同様

の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- ^1H NMR (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.21 (2H, q, $J=7.4\text{ Hz}$), 3.65 (3H, s), 6.37 (1H, t, $J=7.2\text{ Hz}$), 6.42 (1H, s), 7.09 (1H, s), 7.20 (2H, d, $J=8.8\text{ Hz}$), 7.37 (1H, d, $J=6.6\text{ Hz}$), 7.46–7.54 (1H, m), 7.55 (1H, d, $J=6.0\text{ Hz}$), 7.88 (2H, d, $J=8.8\text{ Hz}$), 7.94–8.02 (1H, m), 8.36 (1H, d, $J=7.6\text{ Hz}$), 8.73 (1H, s)
- ESI-MS (m/e): 503 $[\text{M}+\text{H}]$

実施例 275

- 4-(1-メチル-2-オキソ-1,2-ジヒドロ-ピリジン-3-イルオキシ)-6-(4-(プロパン-2-スルホニル)-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

3-ヒドロキシ-1-メチル-1H-ピリジン-2-オン、及び4-(プロパン-2-スルホニル)-フェノールを順次用いて、実施例 274 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- ^1H NMR (CD_3OD) δ : 1.27 (6H, d, $J=6.8\text{ Hz}$), 3.27–3.38 (1H, m), 3.65 (3H, s), 6.37 (1H, t, $J=7.4\text{ Hz}$), 6.42 (1H, s), 7.10 (1H, s), 7.20 (2H, d, $J=8.8\text{ Hz}$), 7.35–7.45 (1H, m), 7.47–7.54 (1H, m), 7.55 (1H, d, $J=6.8\text{ Hz}$), 7.85 (2H, d, $J=8.8\text{ Hz}$), 7.27–8.03 (1H, m), 8.30–8.40 (1H, m), 8.74 (1H, s)
- ESI-MS (m/e): 517 $[\text{M}+\text{H}]$

実施例 276

4-(2, 6-ジフルオロフェノキシ)-6-(6-エタンスルホニルピ
リジン-3-イルオキシ)-2-(1H-ピラゾール-3-イル)-1H-ベ
ンズイミダゾール

実施例 268 で得られた 3-(2, 6-ジフルオロフェノキシ)-5-
5 (6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1, 2-
ジアミン、及び 1H-ピラゾール-3-カルボキサアルデヒドを用いて、実施
例 202 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせる
ことにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.3
10 7 (2H, q, $J=7.4\text{ Hz}$), 6.28-6.32 (1H, m), 7.0
9 (1H, s), 7.19 (2H, t, $J=8.2\text{ Hz}$), 7.34 (1H,
s), 7.52 (1H, t, $J=4.5\text{ Hz}$), 7.83 (1H, s), 8.
04 (1H, d, $J=8.6\text{ Hz}$), 8.46 (1H, d, $J=2.7\text{ Hz}$)
ESI-MS (m/e): 498 $[\text{M}+\text{H}]$

15

実施例 277

4-(1-メチル-2-オキソ-1, 2-ジヒドロピリジン-3-イルオキ
シ)-6-(4-(N, N-ジメチルアミノスルホニル)-フェノキシ)-
2-ピリジン-2-イル-1H-ベンズイミダゾール

20 3-ヒドロキシ-1-メチル-1H-ピリジン-2-オン、及び 4-(N,
N-ジメチルアミノスルホニル)-フェノールを順次用いて、実施例 274 と
同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ : 2.58 (6H, s), 3.48 (3H,
25 s), 6.21 (1H, t, $J=7.1\text{ Hz}$), 6.31 (1H, s), 6.
91 (1H, s), 7.16 (2H, d, $J=8.8\text{ Hz}$), 7.30 (1H,
d, $J=6.4\text{ Hz}$), 7.52 (1H, dd, $J=7.5, 5.7\text{ Hz}$),
7.60 (1H, d, $J=5.1\text{ Hz}$), 7.71 (2H, d, $J=8.8\text{ Hz}$),
7.99 (1H, td, $J=7.8, 1.6\text{ Hz}$), 8.27 (1H,

d, $J=7.8\text{ Hz}$), 8.73 (1H, d, $J=4.6\text{ Hz}$)

ESI-MS (m/e): 518 [M+H]

実施例 278

5 4-(2-クロロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

(工程 1)

3-(2-クロロフェノキシ)-5-(6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンの合成

- 10 2-クロロフェノール、及び6-エタンスルホニルピリジン-3-オールを順次用いて、実施例 67 (工程 1) 乃至 (工程 4) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色油状物質として得た。

(工程 2)

- 15 4-(2-クロロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾールの製造

- (工程 1) で得られた 3-(2-クロロフェノキシ)-5-(6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンを用いて、実施例 205 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- $^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=6.9\text{ Hz}$), 3.39 (2H, q, $J=6.9\text{ Hz}$), 6.28 (1H, d, $J=2.0\text{ Hz}$), 7.10-7.20 (1H, m), 7.28-7.31 (2H, m), 7.39-7.43 (1H, m), 7.57 (2H, td, $J=8.3, 4.2\text{ Hz}$), 8.05 (1H, d, $J=8.6\text{ Hz}$), 8.48 (1H, d, $J=2.7\text{ Hz}$), 8.72 (1H, d, $J=2.3\text{ Hz}$), 8.79-8.80 (1H, m), 9.58 (1H, s)

ESI-MS (m/e): 508 [M+H]

実施例 279

4-(2-フルオロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

- 5 2-フルオロフェノール、及び6-エタンスルホニルピリジン-3-オールを順次用いて、実施例278と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.39 (2H, q, $J=7.4\text{ Hz}$), 6.40 (1H, s), 7.10-7.20 (1H, m), 7.28-7.34 (4H, m), 7.57 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 8.06 (1H, d, $J=8.6\text{ Hz}$), 8.48 (1H, d, $J=2.7\text{ Hz}$), 8.72 (1H, d, $J=2.3\text{ Hz}$), 8.79-8.80 (1H, m), 9.56 (1H, s)

ESI-MS (m/e): 492 $[\text{M}+\text{H}]$

15

実施例 280

4-(2-トリフルオロメチルフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

- 20 2-トリフルオロメチルフェノール、及び6-エタンスルホニルピリジン-3-オールを順次用いて、実施例278と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 3.40 (2H, q, $J=7.4\text{ Hz}$), 6.50 (1H, d, $J=2.0\text{ Hz}$), 7.24 (2H, d, $J=7.8\text{ Hz}$), 7.38 (1H, t, $J=7.8\text{ Hz}$), 7.59 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 7.64 (1H, t, $J=7.6\text{ Hz}$), 7.81 (1H, d, $J=7.8\text{ Hz}$), 8.06 (1H, d, $J=8.6\text{ Hz}$), 8.50 (1H, d, $J=2.7\text{ Hz}$), 8.71 (1H, d, $J=2.3\text{ Hz}$), 8.78-8.79 (1H, m), 9.

5 4-9. 55 (1H, m)

ESI-MS (m/e) : 542 [M+H]

実施例 281

5 4-(1-メチル-2-オキソ-1, 2-ジヒドロピリジン-3-イルオキシ)-6-(4-シクロプロパンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

3-ヒドロキシ-1-メチル-1H-ピリジン-2-オン、及び4-シクロプロパンスルホニルフェノールを順次用いて、実施例274と同様の方法、
10 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

¹HNMR (DMSO-d₆) δ : 1.01-1.15 (4H, m), 2.81-2.90 (1H, m), 3.51 (3H, s), 6.24 (1H, t, J=7.0 Hz), 6.35 (1H, d, J=2.0 Hz), 6.95 (1H, d, J=2.0 Hz), 7.18 (2H, d, J=9.0 Hz), 7.33 (1H, dd, J=7.5, 1.8 Hz), 7.53-7.57 (1H, m), 7.63 (1H, dd, J=6.8, 1.8 Hz), 7.87 (2H, d, J=9.0 Hz), 8.02 (1H, td, J=7.8, 1.8 Hz), 8.31 (1H, d, J=8.0 Hz), 8.75 (1H, d, J=4.1 Hz)

20 ESI-MS (m/e) : 515 [M+H]

実施例 282

4-(2, 6-ジフルオロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-(1-メチルピラゾール-3-イル)-1H-ベンズイミダゾール

実施例268で得られた3-(2, 6-ジフルオロフェノキシ)-5-(6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミン、及び1H-1-メチルピラゾール-3-カルボン酸を用いて、実施例203と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ

ることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.41 (2H, q, $J=7.4\text{ Hz}$), 4.12 (3H, s), 6.61 (1H, s), 7.19 (1H, d, $J=2.3\text{ Hz}$), 7.22 (1H, s), 7.25 (2H, dd, $J=5.6, 2.3\text{ Hz}$), 7.37–7.43 (1H, m), 7.62 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 7.93 (1H, d, $J=2.3\text{ Hz}$), 8.08–8.09 (1H, m), 8.51 (1H, d, $J=2.3\text{ Hz}$)

ESI-MS (m/e): 512 [$M+H$]

10

実施例 283

4-(3-トリフルオロメチルフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

15 3-トリフルオロメチルフェノール、及び6-エタンスルホニルピリジン-3-オールを順次用いて、実施例278と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 3.39 (2H, q, $J=7.4\text{ Hz}$), 6.39 (1H, s), 7.25–7.37 (5H, m), 7.57 (1H, dd, $J=4.3, 2.2\text{ Hz}$), 8.06 (1H, d, $J=8.6\text{ Hz}$), 8.48 (1H, d, $J=2.7\text{ Hz}$), 8.72 (1H, d, $J=2.7\text{ Hz}$), 8.79 (1H, s), 9.56 (1H, s)

ESI-MS (m/e): 542 [$M+H$]

25

実施例 284

4-(4-トリフルオロメチルフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

4-トリフルオロメチルフェノール、及び6-エタンスルホニルピリジン-3-オールを順次用いて、実施例278と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.26 (3H, t, $J=7.4\text{ Hz}$), 3.40 (2H, q, $J=7.4\text{ Hz}$), 6.80 (1H, s), 7.32 (2H, d, $J=8.6\text{ Hz}$), 7.66-7.64 (1H, m), 7.72 (2H, d, $J=8.6\text{ Hz}$), 8.08 (1H, d, $J=9.0\text{ Hz}$), 8.54-8.56 (1H, m), 8.70-8.73 (1H, m), 8.78 (1H, s), 9.50 (1H, s)

ESI-MS (m/e): 542 [$M+H$]

実施例285

4-(2,3-ジフルオロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

2,3-ジフルオロフェノール、及び6-エタンスルホニルピリジン-3-オールを順次用いて、実施例278と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.3\text{ Hz}$), 3.40 (2H, q, $J=7.3\text{ Hz}$), 6.59 (1H, d, $J=1.6\text{ Hz}$), 7.12-7.18 (4H, m), 7.60 (1H, dd, $J=9.0, 2.7\text{ Hz}$), 8.07 (1H, dd, $J=8.6, 0.8\text{ Hz}$), 8.51 (1H, d, $J=2.3\text{ Hz}$), 8.71 (1H, d, $J=2.3\text{ Hz}$), 8.79 (1H, dd, $J=2.7, 1.4\text{ Hz}$), 9.53 (1H, d, $J=1.6\text{ Hz}$)

ESI-MS (m/e): 510 [$M+H$]

実施例286

4-(2-シアノフェノキシ)-6-(6-メタンスルホニルピリジン-

3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-シアノフェノール、及び6-メタンスルホニル-ピリジン-3-オールを順次用いて、実施例274と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- 5 $^1\text{H NMR}$ (CD_3OD) δ : 3.23 (3H, s), 6.86 (1H, d, J = 2.0 Hz), 7.21 (1H, d, J = 8.2 Hz), 7.33-7.37 (2H, m), 7.62-7.67 (3H, m), 7.84 (1H, d, J = 7.8 Hz), 8.04-8.11 (2H, m), 8.36 (1H, d, J = 7.8 Hz), 8.54 (1H, d, J = 2.7 Hz), 8.82 (1H, d, J = 4.7 Hz)
- 10 ESI-MS (m/e): 484 [M+H]

実施例287

- 15 4-(2,4-ジフルオロフェノキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2,4-ジフルオロフェノール、及び6-エタンスルホニル-ピリジン-3-オールを順次用いて、実施例274と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- 20 $^1\text{H NMR}$ (CD_3OD) δ : 1.11 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.51 (1H, d, J = 2.0 Hz), 7.05-7.10 (2H, m), 7.37-7.39 (1H, m), 7.46-7.59 (3H, m), 7.98-8.02 (2H, m), 8.26 (1H, d, J = 7.8 Hz), 8.56 (1H, d, J = 2.7 Hz), 8.73 (1H, d, J = 4.3 Hz)
- 25 ESI-MS (m/e): 509 [M+H]

実施例288

- 4-(ピリジン-2-イルスルファニル)-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

リジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダ
ゾール

ピリジン-2-チオール及び6-メタンスルホニル-ピリジン-3-オール
を順次用いて、実施例274と同様の方法、これに準じた方法又はこれらと常
5 法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 3.22 (3H, s), 7.03 (1H, d, J
= 8.0 Hz), 7.06-7.10 (1H, m), 7.34 (1H, d, J
= 2.1 Hz), 7.37-7.41 (1H, m), 7.43 (1H, dd,
 J = 8.8, 2.8 Hz), 7.52 (1H, td, J = 7.8, 2.2 H
10 z), 7.64 (1H, d, J = 2.1 Hz), 7.88 (1H, td, J =
7.8, 1.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.39
(1H, d, J = 7.8 Hz), 8.45 (1H, dd, J = 4.9, 1.0
Hz), 8.51 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J =
4.1 Hz)

15 ESI-MS (m/e): 476 $[\text{M}+\text{H}]$

実施例289

4-(2,6-ジフルオロ-フェノキシ)-6-(6-エタンスルホニル-ピ
リジン-3-イルオキシ)-5-フルオロ-2-ピラジン-2-イル-1H-
20 ベンズイミダゾール

2,6-ジフルオロ-フェノール、6-エタンスルホニル-ピリジン-3-
オール、及びピラジン-2-カルボン酸を順次用いて、実施例119と同様の
方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
化合物を淡黄色固体として得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 1.30 and 1.32 (total 3H,
each t, J = 7.4 Hz), 3.38 and 3.40 (total
2H, each q, J = 7.4 Hz), 6.96-7.03 (2H, m),
7.10-7.20 (1H, m), 7.14 and 7.52 (total
1H, each d, J = 6.0 Hz), 7.34 and 7.38 (to

total 1H, each dd, $J=8.6, 2.8\text{ Hz}$), 8.03 and
 8.06 (total 1H, each d, $J=8.6\text{ Hz}$), 8.4
 8 and 8.52 (total 1H, each d, $J=2.8\text{ Hz}$),
 8.55–8.72 (2H, m), 9.38 and 9.62 (total
 5 1H, each d, $J=1.5\text{ Hz}$)
 ESI-MS (m/e): 528 [M+H]

実施例 290

4- (2, 6-ジフルオロフェノキシ) -6- (6-エタンスルホニル-ピ
 10 リジン-3-イルオキシ) -5-フルオロ-2-ピリジン-2-イル-1H-
ベンズイミダゾール

実施例 289 で得られた 3- (2, 6-ジフルオロフェノキシ) -4-フ
 ルオロ-5- (6-エタンスルホニル-ピリジン-3-イルオキシ) -ベンゼ
 ン-1, 2-ジアミンを用いて、実施例 196 (工程 6) と同様の方法、これ
 15 に準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色
 固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.30 (3H, t, $J=7.4\text{ Hz}$), 3.3
 8 (2H, q, $J=7.4\text{ Hz}$), 6.94–7.01 (2H, m), 7.0
 4–7.50 (4H, m), 7.79–7.95 (1H, m), 7.99–8.
 20 07 (1H, m), 8.23 and 8.37 (total 1H, each
 d, $J=7.0\text{ Hz}$), 8.48 (1H, s), 8.60–8.68 (1
 H, m)

ESI-MS (m/e): 527 [M+H]

25 実施例 291

4- (2, 6-ジフルオロフェノキシ) -6- (6-エタンスルホニル-ピ
 リジン-3-イルオキシ) -5-フルオロ-2- (1-メチル-1H-ピラ
ゾール-3-イル) -1H-ベンズイミダゾール

実施例 289 で得られた 3- (2, 6-ジフルオロフェノキシ) -4-フ

ルオロ-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミン、及び1H-1-メチル-ピラゾール-3-カルボン酸を用いて、実施例203と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

5 $^1\text{H NMR}$ (CD_3OD) δ : 1.23 (3H, t, $J=7.4\text{ Hz}$), 3.38 (2H, q, $J=7.4\text{ Hz}$), 4.02 (3H, s), 6.94 (1H, s), 7.01-7.12 (2H, m), 7.14-7.23 (1H, m), 7.29 (1H, d, $J=5.4\text{ Hz}$), 7.51 (1H, d, $J=8.0\text{ Hz}$), 7.70 (1H, s), 8.06 (1H, d, $J=8.6\text{ Hz}$), 8.50 (1H, s)

ESI-MS (m/e): 530 $[\text{M}+\text{H}]$

実施例292

15 4-(2,6-ジフルオロ-フェノキシ)-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-5-フルオロ-2-ピリジン-2-イル-1H-ベンズイミダゾール

2,6-ジフルオロ-フェノール及び6-メタンスルホニル-ピリジン-3-オールを順次用いて、実施例290と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡褐色固体として得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 3.21 (3H, s), 6.98 (2H, t, $J=8.0\text{ Hz}$), 7.05-7.50 (4H, m), 7.80-7.93 (1H, m), 8.03 (1H, t, $J=8.8\text{ Hz}$), 8.23 and 8.37 (total 1H, each d, $J=8.4\text{ Hz}$), 8.47 (1H, s), 8.61 and 8.67 (total 1H, each s)

ESI-MS (m/e): 513 $[\text{M}+\text{H}]$

実施例293

1-(2-(6-(4-(2-ヒドロキシ-エチル)-フェノキシ)-2-ピ

リジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- 4-ブロモフェネチル-アルコールを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
5 を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.05-2.90 (10H, m), 3.00-4.45 (4H, m), 5.20-5.45 (1H, m), 6.80-7.70 (7H, m), 7.85-7.95 (1H, m), 8.20-8.45 (1H, m), 8.50-8.80 (1H, m)

- 10 ESI-MS (m/e): 443 [$\text{M}+\text{H}$]

実施例294

- 1-(2-(6-(4-(5-メチル-[1,3,4]オキサジアゾール-2-イル)-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン
15

2-(4-ブロモフェニル)-5-メチル-[1,3,4]オキサジアゾールを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色油状物質として得た。

- $^1\text{H NMR}$ (CDCl_3) δ : 1.40-2.80 (10H, m), 3.50-3.95 (2H, m), 5.10-5.50 (1H, m), 6.90-7.60 (5H, m), 7.82-8.10 (3H, m), 8.35-8.45 (1H, m), 8.60-8.75 (1H, m)

ESI-MS (m/e): 481 [$\text{M}+\text{H}$]

- 25 実施例295

1-(2-(6-(4-(2-メチル-オキサゾール-5-イル)-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

5-(4-ブロモフェニル)-2-メチル-オキサゾールを用いて、実施

例 1 2 2 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1. 6 6–2. 6 6 (1.0 H, m), 3. 5 3–3. 9 4 (2 H, m), 5. 2 1–5. 5 7 (1 H, m), 6. 9 3–7. 9 2 (9 H, m), 8. 3 0–8. 6 9 (2 H, m), 10. 6 1–10. 9 7 (1 H, m)

ESI-MS (m/e): 480 [M+H]

実施例 2 9 6

10 2-ヒドロキシ-1-(2-(6-(4-メタンスルホニル-1-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

実施例 1 6 3 で得られた 5-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール
15 エナンチオマー B を用いて、実施例 1 6 8 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1. 8 4–2. 1 6 (3 H, m), 2. 2 4–2. 4 3 (1 H, m), 3. 1 2 and 3. 1 4 (total 3 H, each s), 3. 4 9–4. 2 4 (4 H, m), 5. 1 7–5. 3 8 (1 H, m), 7. 2 0–7. 5 8 (5 H, m), 7. 9 3–8. 0 4 (3 H, m), 8. 2 6–8. 3 0 (1 H, m), 8. 7 3 (1 H, s)

ESI-MS (m/e): 493 [M+H]

25 実施例 2 9 7、2 9 8

1-(2-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

1-(2-(6-(5-クロロ-ピリジン-2-イルオキシ)-2-ピリジ

ン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

5-クロロ-2-エタンスルホニル-ピリジンを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、

5 表題化合物をそれぞれ得た。

1-(2-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

10 $^1\text{H NMR}$ (CDCl_3) δ : 1.00-1.34 (3H, m), 1.44-2.41 (7H, m), 3.11-3.89 (4H, m), 5.05-5.47 (1H, m), 6.73-8.72 (9H, m), 10.89-11.47 (1H, m)

ESI-MS (m/e): 492 [M+H]

15

1-(2-(6-(5-クロロ-ピリジン-2-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

20 $^1\text{H NMR}$ (CDCl_3) δ : 1.51-2.33 (7H, m), 3.41-3.90 (2H, m), 5.03-5.45 (1H, m), 6.79-8.67 (9H, m), 10.80-11.00 (1H, m)

ESI-MS (m/e): 434 [M+H]

実施例299

25 5-(4-メタンスルホニル-フェノキシ)-2-ピラジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール エナンチオマーA及びエナンチオマーB

(工程1)

2, 2, 2-トリフルオロ-1-(2-(6-(4-メタンスルホニル-

フェノキシ) - 2 - ピラジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イ
 ル) - ピロリジン - 1 - イル) - エタノンの合成

実施例 162 (工程 6) で得られた 1 - (2 - (4, 5 - ジアミノ - 2 -
 (4 - メタンスルホニル - フェノキシ) - フェニル) - ピロリジン - 1 - イ
 5 ル) - 2, 2, 2 - トリフルオロ - エタノン 53 mg のピリジン 1 ml 溶液に、
 ピラジン - 2 - カルボン酸 14.5 mg、1 - (3 - ジメチルアミノプロピ
 ル) - 3 - エチルカルボジイミド・一塩酸塩 27.0 mg を順次加え、反応液
 を室温にて 3 時間撹拌した。反応液を、飽和食塩水にて希釈、酢酸エチルにて
 抽出した。有機層を合わせて、飽和塩化アンモニウム水溶液、飽和重曹水にて
 10 順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた
 残渣をトルエン 1 ml に溶解し、p - トルエンスルホン酸一水和物 9.9 mg
 を加え、反応液を 120 度にて 6 時間撹拌した。冷却後、反応液を酢酸エチル
 にて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウム
 15 で乾燥した。溶媒を減圧留去し、残渣を分取用薄層クロマトグラフィー (K i
 e s e l g e lTM 60 F₂₅₄、A r t 5744 (メルク社製)、クロロホルム/
 メタノール = 9/1) にて精製し、表題化合物を油状物質として得た。

(工程 2)

5 - (4 - メタンスルホニル - フェノキシ) - 2 - ピラジン - 2 - イル -
 6 - ピロリジン - 2 - イル - 1 H - ベンズイミダゾールの合成
 20 2, 2, 2 - トリフルオロ - 1 - (2 - (6 - (4 - メタンスルホニル -
 フェノキシ) - 2 - ピラジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イ
 ル) - ピロリジン - 1 - イル) - エタノン 40 mg のメタノール 1.6 ml、
 及び水 0.4 ml の混合溶液に、炭酸カリウム 55 mg を加え、反応液を室温
 で一終夜撹拌した。反応液を減圧下濃縮し、残渣に飽和塩化アンモニウム水溶
 25 液を加えた後、クロロホルムで抽出し、無水硫酸マグネシウムで乾燥した。溶
 媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (K i e s e
 l g e lTM 60 F₂₅₄、A r t 5744 (メルク社製)、クロロホルム/メタ
 ノール/アンモニア水 = 90/10/1) にて精製し、表題化合物を油状物質
 として得た。

(工程3)

5- (4-メタンスルホニル-フェノキシ)-2-ピラジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール エナンチオマーA、及びエナンチオマーBの製造

- 5 5- (4-メタンスルホニル-フェノキシ)-2-ピラジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール 7. 2mgを光学分割用カラム (CHIRALPAK AD 2cmφ×25cmL (ダイセル化学工業社製)、移動相: ヘキサン/エタノール/ジエチルアミン 20/80/0. 1、流速: 10ml/min) にて光学分割し、エナンチオマーA (保持時間: 21. 5min)、エナンチオマーB (保持時間: 25. 3min) をそれぞれ黄色油状物質として得た。

実施例300

- 15 1- (2- (6- (4-メタンスルホニル-フェノキシ)-2-ピラジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマーA

- 実施例299で得られた5- (4-メタンスルホニル-フェノキシ)-2-ピラジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール エナンチオマーAを用いて、実施例164と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

- $^1\text{H NMR}$ (CDCl_3) δ : 1. 80-2. 42 (7H, m), 3. 00-3. 09 (3H, m), 3. 57-3. 90 (2H, m), 5. 10-5. 43 (1H, m), 7. 02-8. 00 (6H, m), 8. 57-8. 73 (2H, m), 9. 55-9. 48 (1H, m)

ESI-MS (m/e): 478 [M+H]

実施例301

1- (2- (6- (4-メタンスルホニル-フェノキシ)-2-ピラジン-

2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマーB

実施例299で得られた5-(4-メタンスルホニル-フェノキシ)-2-ピラジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール
 5 エナンチオマーBを用いて、実施例164と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

ESI-MS (m/e) : 478 [M+H]

10 実施例302

1-(2-(6-(6-(プロパン-2-スルホニル)-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

5-クロロ-2-(プロパン-2-スルホニル)-ピリジンを用いて、実施
 15 例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CDCl₃) δ : 1.11-1.40 (6H, m), 1.55-2.43 (7H, m), 3.54-3.89 (3H, m), 5.11-5.48 (1H, m), 6.67-8.72 (9H, m), 11.00-11.69
 20 (1H, m)

ESI-MS (m/e) : 506 [M+H]

実施例303

1-(2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-3-フェニル-プロパン-1-オン

3-フェニル-プロピオン酸を用いて、実施例296と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.10–3.10 (11H, m), 3.40–4.00 (2H, m), 4.90–5.30 (1H, m), 6.80–8.00 (13H, m), 8.30–8.50 (1H, m), 8.60–8.75 (1H, m), 10.50–11.20 (1H, m)

5 ESI-MS (m/e): 567 [M+H]

実施例304

1 – (2 – (6 – (4 – メタンスルホニル – フェノキシ) – 2 – ピリジン – 2 – イル – 3 H – ベンズイミダゾール – 5 – イル) – ピロリジン – 1 – イ
 10 ル) – エタンチオン

実施例163で得られた5 – (4 – メタンスルホニル – フェノキシ) – 2 –
 ピリジン – 2 – イル – 6 – ピロリジン – 2 – イル – 1 H – ベンズイミダゾール
 エナンチオマーB 20 mg のクロロホルム 1 ml 溶液に、エチルジチオアセ
 テート 0.010 ml を加えて、反応液を室温にて一終夜攪拌した。反応液を
 15 クロロホルムにて希釈後、飽和重曹水、飽和食塩水で順次洗浄し、無水硫酸マ
 グネシウムにて乾燥した。溶媒を減圧留去し、残渣を分取用薄層クロマトグラ
 フィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、ク
 ロロホルム/メタノール = 9/1) にて精製し、表題化合物を白色固体として
 得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 1.50–2.80 (7H, m), 3.00–3.20 (3H, m), 3.60–4.40 (2H, m), 5.30–5.50 (1H, m), 7.00–7.60 (5H, m), 7.80–8.00 (3H, m), 8.30–8.50 (1H, m), 8.60–8.75 (1H, m)

ESI-MS (m/e): 493 [M+H]

25

実施例305

2 – フルオロ – 1 – (2 – (6 – (4 – メタンスルホニル – フェノキシ) –
2 – ピリジン – 2 – イル – 3 H – ベンズイミダゾール – 5 – イル) – ピロリジ
ン – 1 – イル) – エタノン

フルオロ酢酸ナトリウムを用いて、実施例168と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.67–2.40 (4H, m), 3.00–3.13 (3H, m), 3.51–4.00 (2H, m), 4.48–5.06 (2H, m), 5.18–5.46 (1H, m), 7.02–7.69 (5H, m), 7.80–7.98 (3H, m), 8.34–8.44 (1H, m), 8.53–8.70 (1H, m), 10.82–11.12 (1H, m)
ESI-MS (m/e): 495 $[\text{M}+\text{H}]$

10 実施例306

1-(2-(2-(5-ブロモピリジン-2-イル)-6-(4-メタンスルホニルフェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

(工程1)

15 4-ブロモ-5-(4-メタンスルホニルフェノキシ)-2-ニトロフェニルアミンの合成

4-ブロモ-5-フルオロ-2-ニトロフェニルアミン6.4gのN,N-ジメチルホルムアミド50ml溶液に、4-メタンスルホニルフェノール5.2g、炭酸カリウム5.7gを順次加え、反応液を120度にて3時間攪拌した。反応液に水200mlを加え、析出した固体を濾取および乾燥し、表題化合物を褐色固体として得た。

(工程2)

2-(4-アミノ-2-(4-メタンスルホニルフェノキシ)-5-ニトロフェニル)-ピロール-1-カルボン酸 t-ブチルエステルの合成

25 4-ブロモ-5-(4-メタンスルホニルフェノキシ)-2-ニトロフェニルアミン10.3gのジメトキシエタン100ml溶液に、1-(t-ブトキシカルボニル)ピロール-2-ボロン酸7.9g、ジクロロビストリフェニルホスフィンパラジウム1.8g、飽和炭酸ナトリウム水溶液50ml及び水50mlを順次加え、反応液を窒素雰囲気下、80度にて1時間攪拌し

た。冷却後、反応液をセライト濾過し、濾液を酢酸エチルにて希釈、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／1）により精製し、表題化合物を褐色油状物質として得た。

（工程3）

2-（4，5-ジアミノ-2-（4-メタンスルホニル-フェノキシ）-フェニル）-ピロリジン-1-カルボン酸 t-ブチルエステルの合成

2-（4-アミノ-2-（4-メタンスルホニル-フェノキシ）-5-ニトロ-フェニル）-ピロール-1-カルボン酸 t-ブチルエステル 12 g の2-プロパノール 200 ml 溶液に、水 20 ml、5%白金-炭素触媒 4 g を加え、反応液を 50 kgf/cm² の水素圧雰囲気下、70度にて2日間攪拌した。触媒をセライトにて濾去後、溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝50／1）により精製し、表題化合物を暗褐色油状物質として得た。

（工程4）

2-（5-プロモ-ピリジン-2-イル）-5-（4-メタンスルホニル-フェノキシ）-6-ピロリジン-2-イル-1H-ベンズイミダゾールの合成

2-（4，5-ジアミノ-2-（4-メタンスルホニル-フェノキシ）-フェニル）-ピロリジン-1-カルボン酸 t-ブチルエステル 500 mg のピリジン 10 ml 溶液に、5-プロモピリジン-2-カルボン酸 220 mg、1-（3-ジメチルアミノプロピル）-3-エチルカルボジイミド・一塩酸塩 260 mg を順次加え、反応液を室温にて12時間攪拌した。反応液をクロロホルムにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をトリフルオロ酢酸 10 ml に溶解し、反応液を3時間加熱還流した。冷却後、反応液を減圧留去し、得られた残渣をクロロホルムにて希釈し、飽和重曹水にて塩基性とした後、有機層を飽和食塩水にて洗浄、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム

ム／メタノール／アンモニア水＝５０／１／０．１）により精製し、表題化合物を無色油状物質として得た。

（工程５）

１－（２－（２－（５－プロモ－ピリジン－２－イル）－６－（４－メタン
 5 スルホニル－フェノキシ）－３Ｈ－ベンズイミダゾール－５－イル）－ピロリ
 ジン－１－イル）－エタノンの製造

２－（５－プロモ－ピリジン－２－イル）－５－（４－メタンスルホニル－
 フェノキシ）－６－ピロリジン－２－イル－１Ｈ－ベンズイミダゾール 220
 mg のピリジン 2 ml 溶液に、無水酢酸 0.050 ml を加え、反応液を室温
 10 にて 30 分間攪拌した。反応液をクロロホルムにて希釈し、水、飽和食塩水に
 て順次洗浄後、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得ら
 れた残渣をシリカゲルカラムクロマトグラフィー（クロロホルム／メタノール
 ／アンモニア水＝５０／１／０．１）にて精製し、表題化合物を淡褐色固体と
 して得た。

15 $^1\text{H NMR}$ (CDCl_3) δ : 1.60–2.40 (7H, m), 2.90–3.
 15 (3H, m), 3.50–3.90 (2H, m), 5.05–5.50
 (1H, m), 6.80–7.80 (4H, m), 7.80–8.05 (3H,
 m), 8.20–8.35 (1H, m), 8.60–8.80 (1H, m),
 10.50–11.05 (1H, m)

20 ESI-MS (m/e): 555, 557 [$M+H$]

実施例 307

1－（２－（２－（６－フルオロ－ピリジン－２－イル）－６－（４－メタン
 スルホニル－フェノキシ）－３Ｈ－ベンズイミダゾール－５－イル）－ピロリ
 25 ジン－１－イル）－エタノン

２－（４，５－ジアミノ－２－（４－メタンスルホニル－フェノキシ）－
 フェニル）－ピロリジン－１－カルボン酸 t －ブチルエステル、及び 6－フ
 ルオロ－ピリジン－２－カルボン酸を用いて、実施例 306（工程 4）、（工
 程 5）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせるこ

とにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.70–2.40 (7H, m), 2.98–3.11 (3H, m), 3.57–3.90 (2H, m), 5.07–5.51 (1H, m), 6.81–8.32 (9H, m), 10.64–11.36 (1H, m)
 ESI-MS (m/e): 495 [M+H]

実施例308

1- (2- (2-ピリジン-2-イル-6- (6-トリフルオロメチル-ピリジン-3-イルオキシ) -3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -エタノン

5-ブロモ-2-トリフルオロメチル-ピリジンを用いて、実施例122と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.89 and 2.14 (total 3H, each s), 1.90–2.20 (3H, m), 2.24–2.50 (1H, m), 3.63–3.99 (2H, m), 5.26–5.40 (1H, m), 7.34–7.63 (4H, m), 7.80–7.86 (1H, m), 7.94–8.02 (1H, m), 8.29–8.37 (1H, m), 8.58–8.59 (1H, m), 8.73–8.78 (1H, m)
 ESI-MS (m/e): 468 [M+H]

実施例309

1- (2- (6- (6-メタンスルホニル-ピリジン-3-イルオキシ) -2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) -ピロリジン-1-イル) -エタノン エナンチオマーA

(工程1)

1- (2- (4, 5-ジアミノ-2-ベンジルオキシフェニル) -ピロリジン-1-イル) -エタノン エナンチオマーA及びエナンチオマーBの合成

実施例 121 (工程 8) で得られた、1-(2-(4,5-ジアミノ-2-ペンジルオキシフェニル)-ピロリジン-1-イル)-エタノン 2.2 g を光学分割用カラム (CHIRALPAK AS 2 cmφ×25 cmL (ダイセル化学工業社製)、移動相:ヘキサン/エタノール 30/70、流速:15 ml/min) にて光学分割し、エナンチオマー A (保持時間:11.43 min)、エナンチオマー B (保持時間:16.32 min) をそれぞれ黒色固体として得た。

(工程 2)

1-(2-(6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマー A の製造

実施例 309 (工程 1) で得られた 1-(2-(4,5-ジアミノ-2-ペンジルオキシフェニル)-ピロリジン-1-イル)-エタノン エナンチオマー A、及び 5-クロロ-2-メタンスルホニル-ピリジンを用いて、実施例 121 (工程 9) 乃至 (工程 12) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80-2.42 (7H, m), 3.16-3.27 (3H, m), 3.57-3.91 (2H, m), 5.14-5.34 (1H, m), 7.04-8.10 (6H, m), 8.31-8.70 (3H, m), 10.59-10.94 (1H, m)

ESI-MS (m/e): 478 [M+H]

実施例 310

1-(2-(6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマー B

実施例 309 (工程 1) で得られた 1-(2-(4,5-ジアミノ-2-ペンジルオキシフェニル)-ピロリジン-1-イル)-エタノン エナンチオマー B を用いて、実施例 309 と同様の方法、これに準じた方法又はこれらと

常法とを組み合わせることにより、表題化合物を油状物質として得た。

ESI-MS (m/e) : 478 [M+H]

実施例 311

5 (2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-ピリジン-2-イル-メタノン

実施例 163 で得られた 5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール
10 エナンチオマー B、及びピリジン-2-カルボン酸を用いて、実施例 296 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60-2.45 (4H, m), 2.91-3.09 (3H, m), 3.71-4.30 (2H, m), 5.44-5.60
15 and 5.91-6.03 (total 1H, each m), 6.77-7.93 (11H, m), 8.10-8.66 (3H, m), 10.82-11.00 (1H, m)

ESI-MS (m/e) : 540 [M+H]

20 実施例 312

(2-フルオロフェニル)-(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-メタノン

実施例 163 で得られた 5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール
25 エナンチオマー B、及び 2-フルオロ安息香酸を用いて、実施例 296 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80-2.51 (4H, m), 2.90-3.

0.8 (3H, m), 3.40–4.08 (2H, m), 4.91–5.02
and 5.46–5.60 (total 1H, each m), 6.5
5–8.69 (15H, m)

ESI-MS (m/e) : 557 [M+H]

5

実施例 313

6-(1-アセチルピロリジン-2-イル)-5-(4-フルオロフェノキ
シ)-2-イソオキサゾール-3-イル-1H-ベンズイミダゾール

10 イソオキサゾール-3-カルバアルデヒドを用いて、実施例 189 と同様な
方法、これに準じた方法又はこれらと常法とを組み合わせることにより表題化
合物を得た。

¹HNMR (CDCl₃) δ : 1.80–2.46 (4H, m), 1.87 and
2.16 (total 3H, each s), 3.58–3.88 (2H,
m), 5.13–5.17 and 5.52–5.55 (total 1H, ea
15 chm), 6.85–7.40 (7H, m), 8.56 (1H, s)

ESI-MS (m/e) : 407 [M+H]

実施例 314

5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イ
20 ル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-カルボニ
トリル

実施例 309 (工程 1) で得られた 1-(2-(4,5-ジアミノ-2-ベ
ンジルオキシフェニル)-ピロリジン-1-イル)-エタノン エナンチオ
マー B、及び 2-シアノ-5-ブromo-ピリジンを用いて、実施例 309 と同
25 様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
表題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1.53–2.42 (7H, m), 3.40–3.
50 (2H, m), 5.07–5.29 (1H, m), 7.00–7.94
(6H, m), 8.28–8.68 (3H, m), 11.00–11.52

(1H, m)

ESI-MS (m/e) : 425 [M+H]

実施例3.15

5 (2-(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-2-オキソエチル)-メチルカルバミン酸 t-ブチルエステル

実施例163で得られた5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール
10 エナンチオマーB、およびN-t-ブトキシカルボニルグリシンを用いて、
実施例171と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CDCl₃) δ : 1.20-1.69 (16H, m), 2.76-3.12 (7H, m), 5.15-5.26 (1H, m), 7.00-7.44 (5H, m), 7.76-8.00 (4H, m), 8.28-8.40 (1H, m), 8.58-8.73 (1H, m)

ESI-MS (m/e) : 606 [M+H]

実施例3.16

20 1-(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-2-メチルアミノエタノン

実施例3.15で得られた(2-(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-2-オキソエチル)-メチルカルバミン酸
25 t-ブチルエステルを用いて、実施例171と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CDCl₃) δ : 1.60-1.97 (4H, m), 2.20-2.46 (3H, m), 2.94-3.08 (5H, m), 3.19-3.90

(2H, m), 5.15–5.43 (1H, m), 7.08–7.65 (5H, m), 7.87–7.94 (3H, m), 8.36–8.38 (1H, m), 8.64 (1H, s)

ESI-MS (m/e) : 506 [M+H]

5

実施例317

1-(2-(6-(4-メタンスルホニルフェノキシ)-2-(1H-ピラゾール-3-イル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

10 (工程1)

2-(6-(4-メタンスルホニルフェノキシ)-2-(1H-ピラゾール-3-イル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸 t-ブチルエステルの合成

15 実施例306(工程3)で得られた2-(4,5-ジアミノ-2-(4-メタンスルホニルフェノキシ)-フェニル)-ピロリジン-1-カルボン酸 t-ブチルエステル49.0mgのN,N-ジメチルホルムアミド1ml溶液に、1H-ピラゾール-3-カルボキサルデヒド10.0mgを加え、反応液を90度で一終夜撹拌した。冷却後、反応液を酢酸エチルにて希釈し、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー(Kieselgel™60F₂₅₄、
20 Art 5744(メルク社製)、クロロホルム/メタノール=9/1)にて精製し、表題化合物を褐色固体として得た。

(工程2)

1-(2-(6-(4-メタンスルホニルフェノキシ)-2-(1H-ピラゾール-3-イル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンの製造

2-(6-(4-メタンスルホニルフェノキシ)-2-(1H-ピラゾール-3-イル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸 t-ブチルエステル49.2mgを4N塩酸-ジオキサン1ml

に溶解し、反応液を室温にて2時間攪拌した。反応溶媒を減圧留去し、得られた残渣のピリジン溶液2mlに、無水酢酸0.012mlを加え、30分間室温にて攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60F₂₅₄, Art 5744 (メルク社製)、
 5 クロロホルム/メタノール=9/1) にて精製し、表題化合物を褐色固体として得た。

¹HNMR (CDCl₃) δ: 1.53–2.38 (7H, m), 2.97–3.10 (3H, s), 3.39–3.99 (2H, m), 5.06–5.31 (1H, m), 6.80–8.04 (8H, m)

10 ESI-MS (m/e): 466 [M+H]

実施例318

1-(2-(6-(4-メタンスルホニルフェノキシ)-2-(1-メチル-1H-ピラゾール-3-イル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン
 15

実施例306 (工程3) で得られた2-(4,5-ジアミノ-2-(4-メタンスルホニルフェノキシ)-フェニル)-ピロリジン-1-カルボン酸 t-ブチルエステル、及び1-メチル-1H-ピラゾール-3-カルボン酸を用いて、実施例306 (工程4)、(工程5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。
 20

¹HNMR (CDCl₃) δ: 1.70–2.37 (7H, m), 2.98–3.11 (3H, m), 3.52–4.02 (5H, m), 5.04–5.43 (1H, m), 6.74–7.67 (6H, m), 7.79–7.97 (2H, m), 10.38–11.00 (1H, m)
 25

ESI-MS (m/e): 480 [M+H]

実施例319

1-(2-(2-(5-フルオロピリジン-2-イル)-6-(4-メタン

スルホニル-フェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

5 5-フルオロ-ピリジン-2-カルボン酸を用いて、実施例318と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60–2.50 (7H, m), 2.85–3.20 (3H, m), 3.50–4.00 (2H, m), 5.00–5.50 (1H, m), 6.80–8.10 (7H, m), 8.20–8.60 (2H, m), 10.50–11.20 (1H, m)

10 ESI-MS (m/e): 495 [M+H]

実施例320

(1-アミノ-シクロプロピル)-(2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-メタノン

1-アミノ-シクロプロパンカルボン酸を用いて、実施例168と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

20 $^1\text{H NMR}$ (CD_3OD) δ : 0.80–1.10 (4H, m), 1.88–2.17 (3H, m), 2.32–2.40 (1H, m), 3.12 (3H, s), 4.06 (2H, brs), 5.21 (1H, brs), 7.18–7.54 (5H, m), 7.91–7.99 (3H, m), 8.27 (1H, d, $J=8.0\text{ Hz}$), 8.73 (1H, d, $J=4.3\text{ Hz}$)

ESI-MS (m/e): 518 [M+H]

25

実施例321

5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピラジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-カルボニトリル

実施例 309 (工程 1) で得られた 1-(2-(4,5-ジアミノ-2-ベン
 ジルオキシフェニル)-ピロリジン-1-イル)-エタノン エナンチオ
 マー B、及びピラジン-2-カルボキサアルデヒドを用いて、実施 121 (工
 程 9) 乃至 (工程 12) および実施例 314 と同様の方法、これに準じた方法
 5 又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として
 得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.67-2.47 (7H, m), 3.60-3.
 92 (2H, m), 5.11-5.35 (1H, m), 7.00-7.77
 (4H, m), 8.47-8.73 (3H, m), 9.52-9.68 (1H,
 10 m), 10.88-11.94 (1H, m)
 ESI-MS (m/e): 426 [M+H]

実施例 322

1-(2-(2-(5-シアノーピリジン-2-イル)-6-(4-メタンス
 15 ルホニルフェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジ
ン-1-イル)-エタノン

5-シアノーピリジン-2-カルボン酸を用いて、実施例 307 と同様の方
 法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化
 合物を白色固体として得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 1.05-2.40 (7H, m), 2.80-3.
 20 (3H, m), 3.60-4.00 (2H, m), 5.05-5.45
 (1H, m), 6.90-7.80 (4H, m), 7.80-8.00 (2H,
 m), 8.05-8.20 (1H, m), 8.40-8.60 (1H, m),
 8.80-9.00 (1H, m), 10.40-10.80 (1H, m)
 25 ESI-MS (m/e): 502 [M+H]

実施例 323

1-(2-(2-(4-クロロピリジン-2-イル)-6-(4-メタンス
ルホニルフェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジ

ン-1-イル)-エタノン

4-クロロピリジン-2-カルボン酸を用いて、実施例307と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 5 $^1\text{H NMR}$ (CDCl_3) δ : 1.67–2.40 (7H, m), 3.00–3.13 (3H, m), 3.54–3.91 (2H, m), 5.10–5.44 (1H, m), 6.79–7.52 (5H, m), 7.64–7.97 (2H, m), 8.36–8.57 (2H, m), 10.75–11.24 (1H, m)
- 10 ESI-MS (m/e): 511 [M+H]

実施例324

1-(2-(2-(5-エトキシピリジン-2-イル)-6-(4-メタンスルホニルフェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- 5-エトキシピリジン-2-カルボン酸を用いて、実施例307と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。
- 20 $^1\text{H NMR}$ (CDCl_3) δ : 2.00–3.40 (10H, m), 3.60–4.00 (3H, m), 4.20–5.20 (4H, m), 5.80–6.40 (1H, m), 7.20–9.20 (9H, m), 11.50–12.00 (1H, m)

ESI-MS (m/e): 521 [M+H]

25 実施例325

トランス-1-(4-アセトキシ-2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

(工程1)

1 - (2-フルオロ-4-ニトロフェニル) - 3-ブテン-1-オール
の合成

US 6 2 3 9 1 5 2に記載されている方法に従って合成した4-ニトロ-
2-フルオロベンズアルデヒド2.00gのクロロホルム12ml溶液に、
5 四塩化チタン0.65mlを加え、反応液を室温にて10分間攪拌した後、ア
リルトリメチルシラン2.4mlを加え、反応液を室温にて20分間攪拌
した。反応液を酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水
硫酸ナトリウムで乾燥した。溶媒を減圧留去し、残渣をシリカゲルカラムクロ
マトグラフィー（展開溶媒：ヘキサン/酢酸エチル=3/1）にて精製し、表
10 題化合物を橙色固体として得た。

（工程2）

N - (1 - (2-フルオロ-4-ニトロフェニル) - 3-ブテニル) - ア
セトアミドの合成

1 - (2-フルオロ-4-ニトロフェニル) - 3-ブテン-1-オール4
15 80mgのクロロホルム10ml溶液に、メタンスルホニルクロリド0.29
ml及びトリエチルアミン0.63mlを加えた後、反応液を室温にて15分
間攪拌した。反応液を水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒
を減圧留去し、粗生成物を淡黄色油状物質として得た。粗生成物のジメチルホ
ルムアミド10ml溶液に、アジ化ナトリウム310mgを加え、反応液を4
20 5度にて30分間攪拌した。反応液を酢酸エチルにて希釈し、水にて洗浄後、
無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、粗生成物を褐色油状物質
として得た。得られた粗生成物のテトラヒドロフラン10ml溶液に、トリ
フェニルホスフィン1.0g及び水2mlを加え、反応液を加熱還流下12時
間攪拌した。反応液に1規定塩酸を加え、有機層を除去した後、1規定水酸化
25 ナトリウム水溶液を用いて、水層を塩基性にした。クロロホルムにて抽出し、
無水硫酸ナトリウムで乾燥した後、溶媒を減圧留去し、粗生成物380mgを
褐色油状物質として得た。粗生成物380mgのクロロホルム10ml溶液に、
トリエチルアミン0.50ml、無水酢酸0.25ml及び4-ジメチルアミ
ノピリジン20mgを加え、反応液を室温にて30分間攪拌した。溶媒を減圧

留去し、残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝50／1）にて精製し、表題化合物を褐色油状物質として得た。

（工程3）

5 1-アセチル-2-(2-フルオロ-4-ニトロフェニル)-4-ヒドロキシピロリジンの合成

 N-(1-(2-フルオロ-4-ニトロフェニル)-3-ブテニル)-アセトアミド200mgのテトラヒドロフラン4ml溶液に、水1ml及びヨウ素600mgを加えた後、反応液を室温にて一終夜攪拌した。反応液をクロロホルムで希釈し、飽和重曹水、飽和チオ硫酸ナトリウム水溶液、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、粗生成物を得た。粗生成物のクロロホルム5ml溶液に、トリエチルアミン0.25ml、無水酢酸0.13ml及び4-ジメチルアミノピリジン10mgを加え、反応液を室温にて15分間攪拌した。溶媒を減圧留去し、得られた残渣のメタノール5ml溶液に、炭酸カリウム20mgを加え、反応液を室温にて15分間攪拌した。溶媒を減圧留去した後、残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝30／1）にて精製し、表題化合物を無色固体のジアステレオマー混合物として得た。

10

15

（工程4）

20 1-アセチル-2-(2-フルオロ-4-((ピリジン-2-カルボニル)-アミノ)-フェニル)-4-アセトキシピロリジンの合成

 1-アセチル-2-(2-フルオロ-4-ニトロフェニル)-4-ヒドロキシピロリジン140mgのピリジン2ml溶液に、無水酢酸0.06mlを加え、反応液を50度にて一終夜攪拌した。溶媒を減圧留去し、残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：酢酸エチル）にて精製し、生成物150mgを得た。生成物57mgのメタノール3ml溶液に、展開ラネーニッケル触媒約50mgを加え、反応液を水素雰囲気下、30分間攪拌した後、触媒を濾去し、溶媒を減圧留去した。残渣のピリジン2ml溶液に、ピリジン-2-カルボン酸30mg及び1-(3-ジメチルアミノプロピル)-3-

25

エチルカルボジイミド・一塩酸塩 50 mg を加え、反応液を室温にて一終夜攪拌した。反応液を、酢酸エチルにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を黄色油状物質として得た。

5 (工程 5)

トランス-1-アセチル-2-(5-ニトロ-2-フルオロ-4-(ピリジン-2-カルボニル)-アミノ)-フェニル)-4-アセトキシ-ピロリジン及びシス-1-アセチル-2-(5-ニトロ-2-フルオロ-4-(ピリジン-2-カルボニル)-アミノ)-フェニル)-4-アセトキシ-ピロリジ

10 ンの合成

1-アセチル-2-(2-フルオロ-4-(ピリジン-2-カルボニル)-アミノ)-フェニル)-4-アセトキシ-ピロリジン 36 mg のトリフルオロ酢酸 0.5 ml 溶液に、発煙硝酸 0.1 ml を加え、反応液を室温にて 1 時間攪拌した。溶媒を減圧留去した後、残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: クロロホルム/メタノール = 15/1) にて精製し、表題化合物のジアステレオマー混合物 30 mg を白色固体として得た。さらに、得られたジアステレオマー混合物を分取用薄層クロマトグラフィー (Kiesel gel TM 60 F 254, Art 5744 (メルク社製)、クロロホルム/メタノール = 15/1) にて精製し、表題化合物の単一のジアステレオマーを、それぞれ黄色固体として得た。(Rf 値: トランス体 > シス体)

(工程 6)

トランス-1-(4-アセトキシ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノールの製造

25 トランス-1-アセチル-2-(5-ニトロ-2-フルオロ-4-(ピリジン-2-カルボニル)-アミノ)-フェニル)-4-アセトキシ-ピロリジン 21 mg のジメチルホルムアミド 0.5 ml 溶液に、4-メタンスルホニル-フェノール 10 mg、及び炭酸セシウム 20 mg を加え、反応液を 90 度にて 1 時間攪拌した。塩化スズ (II) 二水和物 100 mg を加え、反応液を

90度にて5時間攪拌した。反応液を酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を黄色油状物質として得た。

^1H NMR (CD_3OD) δ : 1.50–1.90 (3H, m), 2.10–2.53 (2H, m), 2.98 (3H, s), 3.60–3.90 (2H, m), 5.13–5.26 (2H, m), 7.03–7.65 (5H, m), 7.78–7.87 (3H, m), 8.10–8.18 (1H, m), 8.59 (1H, s)

ESI-MS (m/e): 535 [M+H]

10

実施例326

トランス-1-(4-ヒドロキシ-2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

15 実施例325で得られたトランス-1-(4-アセトキシ-2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン40mgのメタノール2ml溶液に、25%ナトリウムメトキシド0.015mlを加え、反応液を室温にて10分間攪拌した。溶媒を減圧留去し、残渣を逆相中圧

20 液体クロマトグラフィー [ODS-AS-360-CC (YMC社製) 移動相: 水-アセトニトリル-0.1%トリフルオロ酢酸] にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去することで、表題化合物を白色固体として得た。

25 ^1H NMR (CD_3OD) δ : 1.48–2.80 (5H, m), 2.99–3.10 (3H, m), 3.48–4.10 (2H, m), 4.40–4.60 (1H, m), 5.25–5.50 (1H, m), 7.00–7.50 (5H, m), 7.75–8.00 (3H, m), 8.24–8.48 (1H, m), 8.48–8.70 (1H, m), 10.70–11.20 (1H, m)

ESI-MS (m/e) : 493 [M+H]

実施例 327

5 シス-1-(4-フルオロ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

実施例 326 で得られたトランス-1-(4-ヒドロキシ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン 10 mg のクロロホルム 1 ml 溶液に、ビス(2-メトキシエチル)アミノサルファートリフロライド 0.02 ml を加え、反応液を室温にて 10 分間攪拌した。溶媒を減圧留去し、残渣を分取用薄層クロマトグラフィー (Kieselgel TM 60 F254, Art 5744 (メルク社製)、クロロホルム/メタノール=15/1) にて精製し、表題化合物を白色固体として得た。

15 $^1\text{H NMR}$ (CD_3OD) δ : 1.92 (3H x 1/2, s), 2.22 (3H x 1/2, s), 2.22-2.80 (2H, m), 3.13 (3H x 1/2, s), 3.15 (3H x 1/2, s), 3.80-4.40 (2H, m), 5.20-5.50 (2H, m), 7.20-7.80 (5H, m), 7.90-8.10 (3H, m), 8.28 (1H, t, $J=7.8\text{ Hz}$), 8.74
20 (1H, brs)

ESI-MS (m/e) : 495 [M+H]

実施例 328

25 シス-1-(4-アセトキシ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

実施例 325 (工程 5) で得られたシス-1-アセチル-2-(5-ニトロ-2-フルオロ-4-((ピリジン-2-カルボニル)-アミノ)-フェニル)-4-アセトキシーピロリジンを用いて、実施例 325 (工程 6) と同様

の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.40–1.90 (3H, m), 2.20–2.55 (2H, m), 3.00 (3H, s), 3.62–3.90 (2H, m),
 5 5.12–5.28 (2H, m), 6.98–7.75 (5H, m), 7.78–7.88 (3H, m), 8.11–8.19 (1H, m), 8.60 (1H, s)

ESI-MS (m/e): 535 [$M+H$]

10 実施例 329

シス-1-(4-ヒドロキシ-2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

実施例 328 で得られたシス-1-(4-アセトキシ-2-(6-(4-メ
 15 タンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミ
 ダゾール-5-イル)-ピロリジン-1-イル)-エタノンを用いて、実施例
 326 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.80–2.00 (3H, m), 2.04–2.
 20 75 (2H, m), 3.12–3.16 (3H, m), 3.40–4.00
 (2H, m), 4.45–4.55 (1H, m), 5.25–5.43 (1H,
 m), 7.18–7.42 (3H, m), 7.50–7.59 (1H, m),
 7.62–7.77 (1H, m), 7.90–8.08 (3H, m), 8.2
 4–8.32 (1H, m), 8.75–8.81 (1H, m)

25 ESI-MS (m/e): 493 [$M+H$]

実施例 330

トランス-1-(4-フルオロ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- 5 シス-1-(4-ヒドロキシ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンを用いて、実施例327と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- $^1\text{H NMR}$ (CD_3OD) δ : 1.70-2.73 (5H, m), 3.11-3.37 (3H, m), 3.62-4.51 (2H, m), 5.24-5.45 (2H, m), 7.13-7.76 (5H, m), 7.94-8.00 (3H, m), 8.28-8.33 (1H, m), 8.73-8.79 (1H, m)
ESI-MS (m/e): 495 [$\text{M}+\text{H}$]

15 実施例331

1-(4-オキソ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

- 塩化オキザリル0.003mlのクロロホルム1ml溶液に、-50度にてジメチルスルホキシド0.003mlを加え、反応液を同温度にて5分間攪拌した。反応液に、実施例326で得られたトランス-1-(4-ヒドロキシ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン6.7mgのクロロホルム1ml溶液を加えた後、反応液を-50度にて
25 15分間攪拌した。トリエチルアミン0.02mlを加え、反応液を室温にて5分間攪拌した後、反応液を酢酸エチルで希釈し、飽和塩化アンモニウム水溶液、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、残渣を逆相中圧液体クロマトグラフィー[ODS-AS-360-C, C (YMC社製) 移動相: 水-アセトニトリル-0.1%トリフルオロ酢酸]

にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去することで、表題化合物を白色固体として得た。

^1H NMR (CD₃OD) δ : 2.03 (3H, s), 2.68 (2H, s),
 5 3.16 (3H, s), 4.09–4.22 (2H, m), 5.70–5.77 (1H, m), 7.05–7.80 (5H, m), 7.94–8.01 (3H, m), 8.24–8.32 (1H, m), 8.72–8.77 (1H, m)

ESI-MS (m/e): 491 [M+H]

10

実施例 332

1-(4,4-ジフルオロ-2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

15 (工程1)

1-アセチル-2-(2-フルオロ-4-ニトロフェニル)-4,4-ジフルオロピロリジンの合成

塩化オキザリル 0.035 ml のクロロホルム 3 ml 溶液に、-50度にてジメチルスルホキシド 0.035 ml を加え、反応液を同温度にて5分間攪拌した。反応液に、実施例 325 (工程3) で得られた 1-アセチル-2-(2-フルオロ-4-ニトロフェニル)-4-ヒドロキシピロリジン 40 mg のクロロホルム 2 ml 溶液を加えた後、反応液を-50度にて10分間攪拌した。トリエチルアミン 0.10 ml を加え、反応液を室温にて5分間攪拌した後、反応液を酢酸エチルで希釈し、飽和塩化アンモニウム水溶液、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のクロロホルム 1 ml 溶液に、ビス(2-メトキシエチル)アミノサルファートリフロライド 0.06 ml を加え、反応液を70度にて一終夜攪拌した。溶媒を減圧留去し、残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=1/1)にて精製し、表題化合物を得た。

25

(工程2)

1 - (4, 4-ジフルオロ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンの製造

- 5 (工程1)で得られた1-アセチル-2-(2-フルオロ-4-ニトロ-フェニル)-4, 4-ジフルオロ-ピロリジンを用いて、実施例325(工程4)～(工程6)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 2.03 (3H x 1/2, s), 2.05 (3H x 1/2, s), 2.50-2.63 (1H, m), 2.85-3.15 (1H, m), 3.14 (3H x 1/2, s), 3.15 (3H x 1/2, s), 3.95-4.25 (2H, m), 5.44-5.58 (1H, m), 7.22-7.29 (2H, m), 7.26-7.42 (1H, m), 7.48-7.54 (1H, m), 7.61-7.68 (1H, m), 7.94-8.04 (3H, m), 8.26-8.32 (1H, m), 8.72-8.77 (1H, m)

ESI-MS (m/e): 513 [$M+H$]

実施例333

- 20 シス-1-(4-フルオロ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマーA、及びエナンチオマーB

実施例327で得られたラセミ体のシス-1-(4-フルオロ-2-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン45mgを、光学分割用カラム(CHIRALPAK AD-H 2cm ϕ ×25cm L(ダイセル化学工業社製)、移動相:ヘキサン/2-プロパノール 30/70、流速:10ml/min)にて光学分割し、エナンチオマーA(保持時

間：18 min)、エナンチオマーB（保持時間：22 min）をそれぞれ白色固体として得た。

エナンチオマーA

ESI-MS (m/e) : 495 [M+H]

5 エナンチオマーB

ESI-MS (m/e) : 495 [M+H]

実施例334

10 6-(6-(1-アセチル-ピロリジン-2-イル)-5-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミダゾール-2-イル)-ニコチン酸メチルエステル

ピロリジン-2, 5-ジカルボン酸-5-メチルエステルを用いて、実施例307と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

15 ¹HNMR (CDCl₃) δ : 1.20-2.40 (7H, m), 2.80-3.20 (3H, m), 3.40-4.00 (2H, m), 3.99 (3H, s), 5.05-5.45 (1H, m), 6.80-7.80 (4H, m), 7.80-8.05 (2H, m), 8.35-8.60 (2H, m), 9.10-9.30 (1H, m), 10.60-11.30 (1H, m)

20 ESI-MS (m/e) : 535 [M+H]

実施例335

25 6-(6-(1-アセチル-ピロリジン-2-イル)-5-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミダゾール-2-イル)-ニコチン酸
 実施例334で得られた6-(6-(1-アセチル-ピロリジン-2-イル)-5-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミダゾール-2-イル)-ニコチン酸メチルエステルを用いて、実施例121（工程6）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (DMSO- d_6) δ : 1.60–2.60 (7H, m), 3.21 (3H, s), 3.60–4.00 (2H, m), 5.00–5.20 (1H, m), 6.90–7.60 (4H, m), 7.80–8.00 (2H, m), 8.30–8.60 (2H, m), 9.20 (1H, s)

5 ESI-MS (m/e): 521 [M+H]

実施例 336

2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸

10 ジメチルアミド

(工程 1)

2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-2,3-ジヒドロ-1H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸 4-ニトロフェニルエステルの合成

15 実施例 163 で得られた 5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾールエナンチオマー B 37 mg のテトラヒドロフラン 1 ml 溶液に、トリエチルアミン 0.060 ml 及び塩化-4-ニトロベンゾイル 21 mg を順次加え、反応液を室温で一終夜攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用
20 薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を白色固体として得た。

(工程 2)

2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸
25 ジメチルアミドの製造

2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-2,3-ジヒドロ-1H-ベンズイミダゾール-5-イル)-ピロリジン-1-カルボン酸 4-ニトロフェニルエステル 20 mg のテトラヒドロフ

ラン1ml溶液に、ジメチルアミン(2.0M テトラヒドロフラン溶液) 1mlを加え、反応液を封管中、100度にて一終夜攪拌した。反応溶媒を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー(ODS-AS-360-CC(YMC社製)移動相:水-アセトニトリル-0.1%トリフルオロ酢酸)にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去することにより、表題化合物を白色固体として得た。

^1H NMR (CD_3OD) δ : 1.80-1.92 (2H, m), 1.94-2.07 (1H, m), 2.33-2.42 (1H, m), 2.80 and 2.85 (total 6H, each brs), 3.12 (3H, s), 3.52-3.58 (1H, m), 3.62-3.78 (1H, m), 5.19-5.26 (1H, m), 7.16-7.80 (5H, m), 7.91-7.99 (3H, m), 8.27 (1H, d, $J=7.6\text{ Hz}$), 8.73 (1H, brs)

ESI-MS (m/e): 506 [M+H]

実施例337

1-(2-(2-(6-ヒドロキシ-ピリジン-2-イル)-6-(4-メタ
ンスルホニル-フェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロ
リジン-1-イル)-エタノン

6-ヒドロキシ-ピリジン-2-カルボン酸を用いて、実施例307と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

^1H NMR (CD_3OD) δ : 1.75-2.47 (7H, m), 2.97-3.26 (4H, m), 3.44-3.96 (2H, m), 5.20-5.40 (1H, m), 6.60-8.05 (10H, m)

ESI-MS (m/e): 493 [M+H]

実施例338

1-(2-(6-(4-フルオロフェニルスルファニル)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

(工程1)

- 5 2-(4-アミノ-2-フルオロフェニル)-ピロール-1-カルボン酸
t-ブチルエステルの合成

4-ブロモ-3-フルオロフェニルアミン1gのジメトキシエタン10m
1溶液に、1-(t-ブトキシカルボニル)ピロール-2-ボロン酸1.6g、
テトラキストリフェニルホスフィンパラジウム200mg、飽和炭酸ナトリウ
ム水溶液5ml及び水5mlを順次加え、反応液を窒素雰囲気下、70度にて
3時間攪拌した。冷却後、反応液をセライト濾過し、濾液を酢酸エチルにて希
釈、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムにて乾燥した。溶
媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開
溶媒：ヘキサン／酢酸エチル＝2／1）により精製し、表題化合物を淡褐色固
15 体として得た。

(工程2)

2-(4-アミノ-2-フルオロフェニル)-ピロリジン-1-カルボン
酸 t-ブチルエステルの合成

2-(4-アミノ-2-フルオロフェニル)-ピロール-1-カルボン酸
20 t-ブチルエステル2.2gの2-プロパノール50ml溶液に、水5ml、
5%白金-炭素触媒660mgを加え、50kgf/cm²の水素圧雰囲気下、
50度にて1日間攪拌した。触媒をセライトにて濾去後、溶媒を減圧留去し、
残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチ
ル＝1／1）にて精製し表題化合物を褐色油状物質として得た。

- 25 (工程3)

ピリジン-2-カルボン酸-(4-(1-アセチル-ピロリジン-2-イル)
)-3-フルオロフェニル)-アミドの合成

2-(4-アミノ-2-フルオロフェニル)-ピロリジン-1-カルボン
酸 t-ブチルエステル181mgのピリジン2ml溶液に、ピリジン-2-

カルボン酸 90 mg、1-(3-ジメチルアミノプロピル)-3-エチルカル
 ボジイミド・一塩酸塩 190 mg を順次加え、反応液を室温にて3時間攪拌し
 た。反応液を、クロロホルムにて希釈し、水、飽和食塩水にて順次洗浄後、無
 水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣 300 mg
 5 に 4 N 塩酸-ジオキサン溶液 2 ml を加え、反応液を室温にて1時間攪拌した。
 反応液を、クロロホルムにて希釈し、飽和重曹水にて塩基性とした後、有機層
 を飽和食塩水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去
 し、得られた残渣のピリジン 1 ml 溶液に、無水酢酸 0.020 ml を加え、
 反応液を室温にて20分間攪拌した。反応液をクロロホルムにて希釈し、水、
 10 飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留
 去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロ
 ロホルム/メタノール=50/1）にて精製し、表題化合物を黄色固体として
 得た。

（工程4）

15 ピリジン-2-カルボン酸-(4-(1-アセチル-ピロリジン-2-イル
)-5-フルオロ-2-ニトロフェニル)-アミドの合成

ピリジン-2-カルボン酸-(4-(1-アセチル-ピロリジン-2-イル
)-3-フルオロフェニル)-アミドのトリフルオロ酢酸 3 ml 溶液に、
 硝酸カリウムを 94 mg 加え、反応液を室温にて2日間攪拌した。反応液を減
 20 圧留去した後、クロロホルムで希釈し、飽和重曹水で塩基性とした後、クロロ
 ホルムにて抽出した。有機層を合わせて、飽和食塩水で洗浄し、無水硫酸マグ
 ネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムク
 ロマトグラフィー（展開溶媒：クロロホルム/メタノール=50/1）にて精
 製し、表題化合物を淡黄色固体として得た。

25 （工程5）

1-(2-(6-(4-フルオロフェニルスルファニル)-2-ピリジ
 ン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル
)-エタノールの製造

ピリジン-2-カルボン酸-(4-(1-アセチル-ピロリジン-2-イル

- ル) - 5 - フルオロ - 2 - ニトロ - フェニル) - アミド 50 mg の N, N - ジメチルホルムアミド 1 ml 溶液に、4 - フルオロ - ベンゼンチオール 20 mg、炭酸カリウム 30 mg を順次加え、反応液を 100 度にて 2 時間攪拌した。反応液に塩化スズ (II) 二水和物 30 mg を加え、反応液をさらに 100 度にて 3 時間攪拌した。冷却後、反応液を飽和重曹水にて希釈し、クロロホルムにて抽出、有機層を無水硫酸マグネシウムにて乾燥し、溶媒を減圧留去した。得られた残渣を分取用薄層クロマトグラフィー (Kieselgel™ 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール = 10/1) にて精製し、表題化合物を白色固体として得た。
- 10 ¹H NMR (CDCl₃) δ : 1.60 - 2.50 (7H, m), 3.60 - 4.00 (2H, m), 5.20 - 5.80 (1H, m), 6.90 - 7.10 (2H, m), 7.15 - 7.80 (5H, m), 7.80 - 8.00 (1H, m), 8.30 - 8.45 (1H, m), 8.55 - 8.70 (1H, m), 10.60 - 11.20 (1H, m)
- 15 ESI-MS (m/e) : 433 [M+H]

実施例 339

- 1 - (2 - (6 - (4 - メタンスルホニル - フェニルスルファニル) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン
- 20

4 - メタンスルホニル - ベンゼンチオールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- ¹H NMR (CDCl₃) δ : 1.40 - 2.45 (7H, m), 2.80 - 3.20 (3H, m), 3.50 - 4.00 (2H, m), 5.20 - 5.65 (1H, m), 7.10 - 8.25 (8H, m), 8.30 - 8.50 (1H, m), 8.50 - 8.80 (1H, m), 10.60 - 11.40 (1H, m)
- 25
- ESI-MS (m/e) : 493 [M+H]

実施例 340

N-(5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-イル)-アセトアミド

(工程 1)

1-(2-(6-(6-アミノ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンの合成

- 10 実施例 121 (工程 10) で得られた 1-(2-(6-ヒドロキシ-2-ピリジン-2-イル-3-(2-トリメチルシラニル-エトキシメチル)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン 5.0 mg のピリジン 1 ml 溶液に、5-ブromo-2-ニトロ-ピリジン 53.5 mg、炭酸セシウム 84.2 mg、酸化銅 (II) 25 mg を加え、反応液
- 15 を封管中 120 度にて一終夜攪拌した。冷却後、反応液に飽和塩化アンモニウム水溶液、飽和食塩水を順次加え、酢酸エチルにて抽出し、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣のエタノール 2 ml 溶液に、ヒドラジン-水和物 0.016 ml、展開ラネ-ニッケル触媒 20 mg を加え、反応液を室温にて 30 分間攪拌した。触媒をセライトにより濾去し、溶媒を減
- 20 圧留去した。得られた残渣を、分取用薄層クロマトグラフィー (Kiesel gelTM 60 F₂₅₄、Art 5744 (メルク社製)、クロロホルム/メタノール=9/1) にて精製し、表題化合物を黄色油状物質として得た。

(工程 2)

- N-(5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-イル)-アセトアミドの製造

1-(2-(6-(6-アミノ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン 13.7 mg のピリジン 1 ml 溶液に、無水酢酸 0.005 m

1を加え、反応液を室温にて3時間攪拌した。反応液を減圧留去し、得られた残渣をトリフルオロ酢酸1mlに溶解し、反応液を室温にて3時間攪拌した。

反応液を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー (ODS-AS-360-CC (YMC社製) 移動相: 水-アセトニトリル-0.

5 1%トリフルオロ酢酸) およびシリカゲルカラムクロマトグラフィー (展開溶媒: クロロホルム/メタノール=9/1) により精製し、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.64-2.44 (10H, m), 3.57-3.91 (2H, m), 5.26-5.62 (1H, m), 6.76-8.74 (10H, m), 10.59-11.31 (1H, m)

ESI-MS (m/e): 457 [M+H]

実施例341

1-(2-(6-(6-アセチル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

1-(5-ブロモ-ピリジン-2-イル)-エタノンを用いて、実施例12と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 1.66-2.42 (7H, m), 2.59-2.74 (3H, m), 3.51-3.90 (2H, m), 5.12-5.45 (1H, m), 6.85-8.10 (6H, m), 8.30-8.70 (3H, m), 10.86-11.24 (1H, m)

ESI-MS (m/e): 442 [M+H]

25

実施例342

2-(5-ブロモ-ピリジン-2-イル)-5-(4-メタンスルホニル-フェノキシ)-6-ピロリジン-2-イル-1H-ベンズイミダゾール エナンチオマーA、及びエナンチオマーB

実施例 306 で得られたラセミ体の 2-(5-ブロモピリジン-2-イル)-5-(4-メタンスルホニルフェノキシ)-6-ピロリジン-2-イル-1H-ベンズイミダゾール 100mg を光学分割用カラム (CHIRAL PAK AD 2cmφ×25cmL (ダイセル化学工業社製)、移動相:ヘキサノール/イソプロパノール/ジエチルアミン 20/80/0.1、流速:10ml/min) にて光学分割し、エナンチオマー A (保持時間:24min)、エナンチオマー B (保持時間:27min) を、それぞれ油状物質として得た。

10 実施例 343

1-(2-(2-(5-ブロモピリジン-2-イル)-6-(4-メタンスルホニルフェノキシ)-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマー A

実施例 342 で得られた 2-(5-ブロモピリジン-2-イル)-5-(4-メタンスルホニルフェノキシ)-6-ピロリジン-2-イル-1H-ベンズイミダゾール エナンチオマー A 43mg のピリジン 1ml 溶液に、無水酢酸 0.020ml を加え、反応液を室温で 10 分間攪拌した。反応液に飽和重曹水を加え、クロロホルムで抽出後、有機層を無水硫酸マグネシウムで乾燥し、溶媒を減圧留去した。得られた残渣を分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を白色固体として得た。
¹H NMR (CDCl₃) δ: 1.60-2.40 (7H, m), 2.80-3.20 (3H, m), 3.50-3.95 (2H, m), 5.05-5.45 (1H, m), 6.90-7.80 (5H, m), 7.80-8.00 (2H, m), 8.10-8.30 (1H, m), 8.60-8.80 (1H, m)
 ESI-MS (m/e): 555, 557 [M+H]

実施例 344

1-(2-(2-(5-ブロモピリジン-2-イル)-6-(4-メタンス

ルホニルーフエノキシ) - 3H-ベンズイミダゾール-5-イル) - ピロリジン-1-イル) - エタノン エナンチオマーB

- 実施例342で得られた2-(5-プロモ-ピリジン-2-イル) - 5-(4-メタンスルホニルーフエノキシ) - 6-ピロリジン-2-イル-1H-
 5 ベンズイミダゾール エナンチオマーBを用いて、実施例343と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

実施例345

- 10 1-(2-(6-(4-メタンスルホニルーフエノキシ) - 2-(5-ビニル-ピリジン-2-イル) - 3H-ベンズイミダゾール-5-イル) - ピロリジン-1-イル) - エタノン

- 5-ビニル-ピリジン-2-カルボン酸を用いて、実施例307と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。
 15

- $^1\text{H NMR}$ (CDCl_3) δ : 1.20-2.40 (7H, m), 2.90-3.15 (3H, m), 3.50-3.90 (2H, m), 5.00-5.45 (1H, m), 5.48 (1H, dd, $J=5.6, 11.2\text{ Hz}$), 5.94 (1H, dd, $J=5.6, 17.6\text{ Hz}$), 6.70-6.85 (1H, m), 7.00-7.25 (2H, m), 7.25-7.80 (2H, m), 7.80-8.00 (3H, m), 8.30-8.40 (1H, m), 8.55-8.70 (1H, m), 10.50-10.80 (1H, m)

ESI-MS (m/e): 503 $[\text{M}+\text{H}]$

- 25 実施例346

1-(2-(6-(6-(1-ヒドロキシ-1-メチル-エチル) - ピリジン-3-イルオキシ) - 2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) - ピロリジン-1-イル) - エタノン

実施例341で得られた1-(2-(6-(6-アセチル-ピリジン-3-

イルオキシ) - 2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) - ピロリジン-1-イル) - エタノン 15.0 mg のテトラヒドロフラン 1.5 ml 溶液に、-78度にてメチルリチウム (1.0 M ジエチルエーテル溶液) 0.1 ml を加え、反応液を-78度にて30分間攪拌した。反応液
 5 を飽和塩化アンモニウム水溶液に注ぎ、クロロホルムにて抽出、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: クロロホルム/メタノール=7.5/1) により精製し、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.46-1.63 (6H, m), 1.63-2.47 (7H, m), 2.87-2.99 and 3.34-3.91 (total 3H, each m), 5.18-5.51 (1H, m), 6.72-7.91 (6H, m), 8.17-8.68 (3H, m), 10.54-10.94 (1H, br)

ESI-MS (m/e): 458 $[\text{M}+\text{H}]$

15

実施例 347

(5-(6-(1-アセチル-ピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イルオキシ)-ピリジン-2-イル)-カルバミン酸 エチルエステル

20 実施例 340 (工程 1) で得られた 1-(2-(6-(6-アミノ-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン 14.4 mg のピリジン 1 ml 溶液に、クロロギ酸エチル 0.003 ml を加え、反応液を室温にて30分間攪拌した。反応液を減圧留去し、得られた残渣をトリフルオロ酢酸 1 ml
 25 に溶解し、反応液を室温にて1時間攪拌した。反応液を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー (ODS-AS-360-CC (YMC社製) 移動相: 水-アセトニトリル-0.1%トリフルオロ酢酸) およびシリカゲルカラムクロマトグラフィー (展開溶媒: クロロホルム/メタノール=9/1) により精製し、表題化合物を黄色油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.14–1.51 (3H, m), 1.52–2.46 (7H, m), 2.78–2.93 and 3.51–3.88 (total 3H, each m), 4.16–4.26 (2H, m), 5.27–5.63 (1H, m), 6.80–8.69 (10H, m)

5 ESI-MS (m/e): 487 [M+H]

実施例348

10 1 – (2 – (6 – (6 – (5 – メチル – [1, 2, 4] オキサジアゾール – 3 – イル) – ピリジン – 3 – イル オキシ) – 2 – ピリジン – 2 – イル – 3 H – ベンズイミダゾール – 5 – イル) – ピロリジン – 1 – イル) – エタノン

5 – ブロモ – 2 – シアノ – ピリジンを用いて、実施例153と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

15 $^1\text{H NMR}$ (CDCl_3) δ : 1.49–2.42 (7H, m), 2.54–2.71 (3H, m), 3.50–3.88 (2H, m), 5.04–5.48 (1H, m), 7.00–8.67 (10H, m)

ESI-MS (m/e): 482 [M+H]

実施例349

20 3 – (2 – (6 – (4 – メタンスルホニル – フェノキシ) – 2 – ピリジン – 2 – イル – 3 H – ベンズイミダゾール – 5 – イル) – ピロリジン – 1 – イル) – 3 – オキソ – プロピオニトリル

シアノ酢酸を用いて、実施例296と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

25 $^1\text{H NMR}$ (CDCl_3) δ : 1.80–2.05 (4H, m), 3.05–3.25 (4H, m), 3.47–3.93 (3H, m), 5.19–5.41 (1H, m), 7.00–7.59 (5H, m), 7.82–7.99 (3H, m), 8.35–8.41 (1H, m), 8.62–8.68 (1H, m)

ESI-MS (m/e): 502 [M+H]

実施例 350

シクロプロピル- (2- (6- (4-メタンスルホニル-フェノキシ) -2-
ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) -ピロリジン-
5 1-イル) -メタノン

シクロプロパンカルボン酸を用いて、実施例 296 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CDCl₃) δ : 0.92-1.08 (4H, m), 1.60-1.
10 66 (2H, m), 1.85-1.99 (2H, m), 2.20-2.38
(1H, m), 3.05-3.08 (3H, m), 3.63-4.00 (2H,
m), 5.33-5.41 (1H, m), 7.12-7.44 (5H, m),
7.86-7.92 (3H, m), 8.40-8.44 (1H, m), 8.6
0-8.68 (1H, m)
15 ESI-MS (m/e) : 503 [M+H]

実施例 351

3, 3, 3-トリフルオロ-1- (2- (6- (4-メタンスルホニル-フェ
ノキシ) -2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イ
20 ル) -ピロリジン-1-イル) -プロパン-1-オン

3, 3, 3-トリフルオロ-プロピオン酸を用いて、実施例 296 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CDCl₃) δ : 1.85-2.40 (4H, m), 2.90-3.
25 27 (5H, m), 3.65-3.90 (2H, m), 5.15-5.43
(1H, m), 6.97-7.63 (5H, m), 7.84-7.96 (3H,
m), 8.38-8.43 (1H, m), 8.60-8.68 (1H, m)
ESI-MS (m/e) : 545 [M+H]

実施例 3 5 2

(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-(テトラヒドロフラン-2-イル)-メタノン

- 5 テトラヒドロフラン-2-カルボン酸を用いて、実施例 2 9 6 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.85-2.33 (7H, m), 3.05-3.10 (3H, m), 3.63-4.08 (5H, m), 4.15-4.62
10 (1H, m), 5.33-5.62 (1H, m), 7.11-7.55 (5H, m), 7.84-7.95 (3H, m), 8.37-8.42 (1H, m), 8.60-8.67 (1H, m)

ESI-MS (m/e): 533 [M+H]

15 実施例 3 5 3

N-(2-(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-2-オキソエチル)-アセトアミド

- 20 アセチルアミノ酢酸を用いて、実施例 2 9 6 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.90-2.05 (8H, m), 3.07-3.09 (3H, m), 3.47-4.01 (3H, m), 5.16-5.40 (1H, m), 6.52-6.70 (1H, m), 7.04-7.20 (2H,
25 m), 7.33-7.57 (2H, m), 7.84-7.98 (3H, m), 8.35-8.38 (1H, m), 8.61-8.67 (1H, m)

ESI-MS (m/e): 534 [M+H]

実施例 3 5 4 (ジアステレオマー A)、3 5 5 (ジアステレオマー B)

1-(1-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノール ジアステレオマーA及びジアステレオマーB

実施例14で得られた5-フルオロ-4-(4-メタンスルホニル-フェノキシ)-2-ニトロ-フェニルアミン、及び1-ピロリジン-2-イル-エタノールを用いて、実施例15と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体のジアステレオマー混合物として得た。得られたジアステレオマー混合物を、さらに分取用薄層クロマトグラフィー (Kieselgel™ 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製することで、ジアステレオマーA、及びBをそれぞれ淡黄色固体として得た。

1-(1-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノール ジアステレオマーA

¹HNMR (CD₃OD) δ: 1.09 (3H, d, J=6.7 Hz), 1.66-1.78 (1H, m), 1.80-1.99 (3H, m), 3.06-3.18 (1H, m), 3.12 (3H, s), 3.61-3.69 (1H, m), 3.78-3.83 (1H, m), 3.90-3.99 (1H, m), 6.97-7.81 (5H, m), 7.89-8.00 (3H, m), 8.26 (1H, d, J=8.2 Hz), 8.74 (1H, d, J=4.7 Hz)

ESI-MS (m/e): 479 [M+H]

1-(1-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノール ジアステレオマーB

¹HNMR (CD₃OD) δ: 0.76 (3H, d, J=6.3 Hz), 1.70-1.82 (3H, m), 1.92-2.00 (1H, m), 3.06-3.13 (1H, m), 3.10 (3H, s), 3.61-3.69 (1H, m), 3.83-3.90 (1H, m), 3.95-4.03 (1H, m), 7.0

4 (2H, d, $J=8.9$ Hz), 7.37–7.44 (2H, m), 7.46–7.49 (1H, m), 7.89 (2H, d, $J=8.9$ Hz), 7.93–7.99 (1H, m), 8.27 (1H, d, $J=7.8$ Hz), 8.74 (1H, d, $J=4.7$ Hz)

5 ESI-MS (m/e): 479 [M+H]

実施例 356

5-(2-(1-フルオロエチル)-ピロリジン-1-イル)-6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

10

実施例 354 で得られた 1-(1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノール ジアステレオマー A 21 mg のクロロホルム 1 ml 溶液に、 -78 度にてジエチルアミノサルファートリフルオリド 0.007 ml を加え、反応液を -78 度にて 1 時間攪拌した。反応液を室温まで昇温後、反応液に飽和重曹水を加えた後、酢酸エチルにて抽出し、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (Kieselgel™ 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ : 1.18 and 1.24 (total 3H, each d, $J=6.3, 6.7$ Hz), 1.53–1.78 (1H, m), 1.83–2.00 (3H, m), 3.11 (3H, s), 3.11–3.20 (1H, m), 3.52–3.61 (1H, m), 3.89–4.01 (1H, m), 4.63–4.87 (1H, m), 7.04 (2H, d, $J=9.0$ Hz), 7.21–7.53 (3H, m), 7.89 (2H, d, $J=9.0$ Hz), 7.96–8.02 (1H, m), 8.27 (1H, d, $J=7.8$ Hz), 8.74 (1H, d, $J=4.7$ Hz)

25

ESI-MS (m/e): 481 [M+H]

実施例 357

5 5 - (2 - (1 - フルオロエチル) - ピロリジン - 1 - イル) - 6 - (4 -
メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイ
ミダゾール

実施例 355 で得られた 1 - (1 - (6 - (4 - メタンスルホニル - フェノ
 キシ) - 2 - ピリジン - 2 - イル - 3H - ベンズイミダゾール - 5 - イル) -
 ピロリジン - 2 - イル) - エタノール ジアステレオマー B を用いて、実施例
 356 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせるこ
 10 とにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 0.99 and 1.09 (total 3H,
 each d, $J=6.5, 6.2\text{ Hz}$), 1.59-1.83 (3H, m),
 1.93-2.03 (1H, m), 3.00-3.10 (1H, m), 3.0
 9 (3H, s), 3.54-3.67 (1H, m), 4.10-4.19 (1
 15 H, m), 4.37-4.54 (1H, m), 7.04 (2H, d, $J=8.$
 9 Hz), 7.36-7.48 (3H, m), 7.86 (2H, d, $J=8.$
 9 Hz), 7.94-7.98 (1H, m), 8.25 (1H, d, $J=7.$
 8 Hz), 8.72 (1H, d, $J=4.7\text{ Hz}$)

ESI-MS (m/e): 481 $[\text{M}+\text{H}]$

20

実施例 358

1 - (1 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン -
2 - イル - 3H - ベンズイミダゾール - 5 - イル) - ピロリジン - 2 - イ
ル) - エタノール

25 塩化メチレン 3 ml に、 -78°C にて塩化オキザリル 0.080 ml 及びジ
 メチルスルホキシド 0.087 ml を順次加え、反応液を -78°C にて 10 分
 間攪拌後、 -78°C にて実施例 354 及び 355 で得られた 1 - (1 - (6 -
 (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3H - ベ
 ンズイミダゾール - 5 - イル) - ピロリジン - 2 - イル) - エタノールのジア

ステレオマー混合物 146 mg の塩化メチレン 2 ml 溶液を加えた。反応液を -78 度にて 30 分間攪拌後、トリエチルアミン 0.42 ml を加え、さらに反応液を -78 度にて 10 分間攪拌後、室温まで昇温した。反応液に飽和塩化アンモニウム水溶液を加え、酢酸エチルにて抽出し、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィ (KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール = 10/1) にて精製し、表題化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ : 1.78–2.07 (3H, m), 1.94 (3H, s), 2.20–2.29 (1H, m), 3.06 (3H, s), 3.37–3.45 (1H, m), 3.64–3.77 (1H, m), 4.27–4.30 (1H, m), 6.80–7.44 (5H, m), 7.80–7.88 (3H, m), 8.27–8.40 (1H, m), 8.61–8.62 (1H, m)

ESI-MS (m/e): 477 [M+H]

実施例 359 (エナンチオマー A)、360 (エナンチオマー B)

1-(1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノン エナンチオマー A、及びエナンチオマー B

実施例 358 で得られたラセミ体の 1-(1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノン 27 mg を光学分割用カラム (CHIRALPAK AD-H 2 cm ϕ \times 25 cm L (ダイセル化学工業社製)、移動相: エタノール、流速: 10 ml/min) にて光学分割し、エナンチオマー A (保持時間: 20.8 min)、エナンチオマー B (保持時間: 46.9 min) をそれぞれ淡黄色固体として得た。

1-(1-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-
2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イ
ル)-エタノン エナンチオマーA

ESI-MS (m/e) : 477 [M+H]

5

1-(1-(6-(4-メタンスルホニル-フェノキシ)-2-ピリジン-
2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イ
ル)-エタノン エナンチオマーB

ESI-MS (m/e) : 477 [M+H]

10

実施例361

1-(1-(6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-
2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジ
ン-2-イル)-エタノン

- 15 実施例196 (工程3) で得られた5-フルオロ-4-(6-メタンスルホ
ニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニルアミン、及び1-
メチル-1-(2-ピロリジニル) エタノールを用いて、実施例354、35
5及び358と同様の方法、これに準じた方法又はこれらと常法とを組み合わ
せることにより、表題化合物を淡黄色固体として得た。

- 20 ^1H NMR (CD_3OD) δ : 1.80-2.10 (3H, m), 2.08 (3
H, s), 2.28-2.39 (1H, m), 3.24 (3H, s), 3.4
0-3.47 (1H, m), 3.66-3.73 (1H, m), 4.46 (1
H, t, $J=7.4\text{ Hz}$), 7.17 (1H, s), 7.40 (1H, s),
7.48 (1H, dd, $J=2.7, 8.8\text{ Hz}$), 7.54 (1H, dd,
25 $J=4.9, 7.6\text{ Hz}$), 8.02 (1H, dt, $J=0.8, 7.8\text{ Hz}$),
8.07 (1H, dd, $J=0.6, 8.8\text{ Hz}$), 8.24 (1H,
d, $J=7.8\text{ Hz}$), 8.46 (1H, dd, $J=0.6, 2.7\text{ Hz}$),
7.78 (1H, dt, $J=0.8, 4.9\text{ Hz}$)

ESI-MS (m/e) : 478 [M+H]

実施例 3 6 2 (エナンチオマー A)、3 6 3 (エナンチオマー B)

1 — (1 — (6 — (6 — メタンスルホニル — ピリジン — 3 — イルオキシ) —
2 — ピリジン — 2 — イル — 3 H — ベンズイミダゾール — 5 — イル) — ピロリジ
5 ン — 2 — イル) — エタノン エナンチオマー A、及びエナンチオマー B

実施例 3 6 1 で得られたラセミ体の 1 — (1 — (6 — (6 — メタンスルホニ
ル — ピリジン — 3 — イルオキシ) — 2 — ピリジン — 2 — イル — 3 H — ベンズイ
ミダゾール — 5 — イル) — ピロリジン — 2 — イル) — エタノン 3 4 mg を光学
分割用カラム (CHIRALPAK AD-H 2 cmφ × 2 5 cmL (ダイ
10 セル化学工業社製)、移動相: エタノール、流速: 1 0 ml/min) にて光
学分割し、エナンチオマー A (保持時間: 2 8. 8 min)、エナンチオマー
B (保持時間: 4 8. 2 min) をそれぞれ淡黄色固体として得た。

1 — (1 — (6 — (6 — メタンスルホニル — ピリジン — 3 — イルオキシ) —
15 2 — ピリジン — 2 — イル — 3 H — ベンズイミダゾール — 5 — イル) — ピロリジ
ン — 2 — イル) — エタノン エナンチオマー A

E S I — M S (m/e) : 4 7 8 [M+H]

1 — (1 — (6 — (6 — メタンスルホニル — ピリジン — 3 — イルオキシ) —
20 2 — ピリジン — 2 — イル — 3 H — ベンズイミダゾール — 5 — イル) — ピロリジ
ン — 2 — イル) — エタノン エナンチオマー B

E S I — M S (m/e) : 4 7 8 [M+H]

実施例 3 6 4

25 (2 S) — 1 — (6 — (4 — メタンスルホニル — フェノキシ) — 2 — ピリジ
ン — 2 — イル — 3 H — ベンズイミダゾール — 5 — イル) — ピロリジン — 2 — カ
ルボキサミド

実施例 1 4 で得られた 5 — フルオロ — 4 — (4 — メタンスルホニル — フェノ
キシ) — 2 — ニトロ — フェニルアミン、及び L — プロリンアミド 塩酸塩を用

いて、実施例15と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.91–2.03 (3H, m), 2.26–2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18–3.28 (1H, m), 3.63–3.91 (1H, m), 4.19–4.23 (1H, m), 6.04–6.13 (1H, m), 6.86–7.28 (4H, m), 7.37–7.41 (1H, m), 7.48–7.54 (1H, m), 7.80–7.92 (3H, m), 8.34–8.38 (1H, m), 8.48–8.63 (1H, m)

ESI-MS (m/e): 478 [M+H]

実施例365

(2R)-1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-カルボキサミド

実施例14で得られた5-フルオロ-4-(4-メタンスルホニルフェノキシ)-2-ニトロフェニルアミン、及びD-プロリンアミドを用いて、実施例15と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.91–2.03 (3H, m), 2.26–2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18–3.28 (1H, m), 3.63–3.91 (1H, m), 4.19–4.23 (1H, m), 6.04–6.13 (1H, m), 6.86–7.28 (4H, m), 7.37–7.41 (1H, m), 7.48–7.54 (1H, m), 7.80–7.92 (3H, m), 8.34–8.38 (1H, m), 8.48–8.63 (1H, m)

ESI-MS (m/e): 478 [M+H]

実施例366

6 - ((3R) - 3 - フルオロ - ピロリジン - 1 - イル) - 5 - (4 - メタン
スルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダ
ゾール

実施例 14 で得られた 5 - フルオロ - 4 - (4 - メタンスルホニル - フェノ
キシ) - 2 - ニトロ - フェニルアミン、及び (R) - 3 - フルオロピロリジン
を用いて、実施例 15 と同様の方法、これに準じた方法又はこれらと常法とを
組み合わせることにより、表題化合物を黄色油状物質として得た。

¹H NMR (CD₃OD) δ : 1.95 - 2.40 (2H, m), 3.10 (3
H, s), 3.25 - 3.73 (4H, m), 5.14 - 5.40 (1H,
10 m), 7.06 (2H, d, J = 8.9 Hz), 7.07 - 7.20 (1H,
m), 7.32 - 7.40 (1H, m), 7.42 - 7.48 (1H, m),
7.89 (2H, d, J = 8.9 Hz), 7.93 - 7.99 (1H, m),
8.23 (1H, d, J = 8.2 Hz), 8.71 (1H, d, J = 5.1 Hz)

15 ESI-MS (m/e) : 453 [M+H]

実施例 367

1 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イ
ル - 3H - ベンズイミダゾール - 5 - イル) - ピロリジン - 3 - カルボキサミ
ド

実施例 14 で得られた 5 - フルオロ - 4 - (4 - メタンスルホニル - フェノ
キシ) - 2 - ニトロ - フェニルアミン、及びピロリジン - 3 - カルボキサミド
を用いて、実施例 15 と同様の方法、これに準じた方法又はこれらと常法とを
組み合わせることにより、表題化合物を得た。

25 ¹H NMR (CDCl₃) δ : 2.03 - 2.30 (2H, m), 2.89 - 2.
99 (1H, m), 3.06 (3H, s), 3.24 - 3.60 (4H, m),
5.70 - 5.86 (2H, m), 7.00 - 7.48 (5H, m), 7.8
0 - 7.90 (3H, m), 8.34 - 8.40 (1H, m), 8.57 - 8.
64 (1H, m)

ESI-MS (m/e) : 478 [M+H]

実施例 368

5 (2R)-1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジ
ン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-カ
ルボン酸 メトキシメチルアミド

実施例 14 で得られた 5-フルオロ-4-(4-メタンスルホニルフェノ
キシ)-2-ニトロフェニルアミン、及び (R)-N-メトキシ-N-メチ
ルピロリンアミドを用いて、実施例 15 と同様の方法、これに準じた方法又は
10 これらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.83-2.05 (3H, m), 2.25-2.
40 (1H, m), 3.09 (3H, brs), 3.13 (3H, s), 3.
40-3.47 (1H, m), 3.68-3.78 (1H, m), 3.84
(3H, brs), 4.90-5.09 (1H, m), 7.06-7.30
15 (4H, m), 7.42-7.50 (1H, m), 7.87-8.00 (3H,
m), 8.19-8.28 (1H, m), 8.70-8.76 (1H, m)

ESI-MS (m/e) : 522 [M+H]

実施例 369

20 (2R)-1-(1-(6-(6-エタンスルホニルピリジン-3-イルオ
キシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-
ピロリジン-2-イル)-エタノン

実施例 221 (工程 2) で得られた 4-(6-エタンスルホニルピリジン
-3-イルオキシ)-5-フルオロ-2-ニトロフェニルアミン及び 1-(
25 R)-ピロリジン-2-イル-エタノールを用いて、実施例 354、355 及
び実施例 358 と同様の方法、これに準じた方法又はこれらと常法とを組み合
わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 1.7
8-2.03 (3H, m), 2.03 (3H, s), 2.22-2.35 (1

H, m), 3.30-3.43 (1H, m), 3.39 (2H, q, J=7.4 Hz), 3.64-3.75 (1H, m), 4.35-4.42 (1H, m), 7.03-7.48 (4H, m), 7.90-7.99 (1H, m), 8.03 (1H, d, J=8.6 Hz), 8.17-8.28 (1H, m),
 5 8.43-8.46 (1H, m), 8.70-8.75 (1H, m)
 ESI-MS (m/e) : 492 [M+H]

実施例 370

(2R)-1-(1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノン

実施例 225 (工程 2) で得られた 4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-5-フルオロ-2-ニトロ-フェニルアミン及び 1-(R)-ピロリジン-2-イル-エタノールを用いて、実施例 205 及び実施例
 15 358 と同様の方法、これに準じた方法又はこれらと常法とを順次組み合わせることにより、表題化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ : 1.24 (3H, t, J=7.4 Hz), 1.80-2.03 (3H, m), 2.04 (3H, s), 2.24-2.34 (1H, m), 3.30-3.45 (1H, m), 3.39 (2H, q, J=7.4 Hz), 3.63-3.74 (1H, m), 4.37-4.44 (1H, m), 7.07 (1H, brs), 7.22-7.50 (2H, m), 8.03-8.05 (1H, m), 8.42-8.46 (1H, m), 8.63-8.66 (1H, m), 8.73 (1H, d, J=1.6 Hz), 9.37-9.43 (1H, m)

25 ESI-MS (m/e) : 493 [M+H]

実施例 371

(2R)-1-(1-(6-(4-エタンスルホニルフェノキシ)-2-ピロリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノン

実施例259(工程1)で得られた4-(4-エタンスルホニルフェノキシ)-5-フルオロ-2-ニトロフェニルアミン及び1-(R)-ピロリジン-2-イル-エタノールを用いて、実施例369と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 1.8
1-2.03 (3H, m), 2.02 (3H, s), 2.24-2.33 (1
H, m), 3.22 (2H, q, $J=7.4\text{ Hz}$), 3.38-3.46 (1
H, m), 3.72-3.79 (1H, m), 4.40 (1H, t, $J=7.$
5 Hz), 7.10-7.12 (3H, m), 7.29 (1H, s), 7.4
5-7.48 (1H, m), 7.87-7.90 (2H, m), 7.90-7.
15 98 (1H, m), 8.24 (1H, d, $J=7.6\text{ Hz}$), 8.72 (1H,
d, $J=4.9\text{ Hz}$)

ESI-MS (m/e): 491 $[\text{M}+\text{H}]$

実施例372

20 (2R)-1-(1-(6-(4-エタンスルホニルフェノキシ)-2-ピラジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-イル)-エタノン

実施例259(工程1)で得られた4-(4-エタンスルホニルフェノキシ)-5-フルオロ-2-ニトロフェニルアミン及び1-(R)-ピロリジン-2-イル-エタノールを用いて、実施例369と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 1.8
2-2.04 (3H, m), 2.04 (3H, s), 2.24-2.34 (1

H, m), 3.22 (2H, q, $J=7.4$ Hz), 3.34–3.50 (1
 H, m), 3.70–3.79 (1H, m), 4.38–4.48 (1H,
 m), 7.00–7.38 (4H, m), 7.89 (2H, d, $J=9.0$ Hz),
 8.66 (1H, br s), 8.75 (1H, dd, $J=1.6, 2.5$
 5 5 Hz), 9.38–9.48 (1H, m)
 ESI-MS (m/e): 492 [M+H]

実施例373

(2R)-1-(1-(6-(6-エタンスルホニル-ピリジン-3-イルオ
 10 キシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-
ピロリジン-2-イル)-プロパン-1-オン

実施例221 (工程2) で得られた5-フルオロ-4-(6-エタンスルホ
 ニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニルアミン、及び1-
 (R)-ピロリジン-2-イル-プロパノールを用いて、実施例369と同様
 15 の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表
 題化合物を淡黄色固体として得た。

^1H NMR (CD_3OD) δ : 0.93 (3H, t, $J=7.2$ Hz), 1.2
 5–1.27 (3H, m), 1.75–2.00 (3H, m), 2.23–2.
 53 (3H, m), 3.33–3.44 (3H, m), 3.71 (2H, q,
 20 $J=7.3$ Hz), 4.43 (1H, t, $J=7.6$ Hz) 7.14 (1H,
 s), 7.38 (1H, s), 7.45–7.50 (2H, m), 7.93–
 8.00 (1H, m), 8.06 (1H, d, $J=8.8$ Hz), 8.25
 (1H, d, $J=8.0$ Hz), 8.45 (1H, d, $J=2.9$ Hz), 8.
 73 (1H, d, $J=4.9$ Hz)
 25 ESI-MS (m/e): 506 [M+H]

実施例374

(2R) - 2 - (1 - (6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 3H - ベンズイミダゾール - 5 - イル) -
ピロリジン - 2 - イル) - プロパン - 2 - オール

実施例 221 (工程 2) で得られた 5 - フルオロ - 4 - (6 - エタンスルホ
 5 ニル - ピリジン - 3 - イルオキシ) - 2 - ニトロ - フェニルアミン、及び
 (R) - 1 - メチル - 1 - (2 - ピロリジニル) エタノールを用いて、実施例
 369 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CD₃OD) δ : 0.85 and 0.87 (total 6H,
 10 each s), 1.22 (3H, t, J = 7.3 Hz), 1.59 - 1.84 (3H, m), 1.93 - 2.05 (1H, m), 3.08 - 3.17 (1H, m), 3.31 - 3.40 (2H, m), 3.53 - 3.61 (1H, m), 4.00 - 4.03 (1H, m), 7.43 - 7.64 (4H, m), 7.91 - 7.98 (1H, m), 8.02 (1H, d, J = 8.8 Hz),
 15 8.25 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 2.7 Hz), 8.71 - 8.73 (1H, m)

ESI-MS (m/e) : 508 [M+H]

実施例 375

20 (2R, 4R) - 4 - ヒドロキシ - 1 - (6 - (4 - メタンスルホニル - フェ
ノキシ) -
2 - ピリジン - 2 - イル - 3H - ベンズイミダゾール - 5 - イル) - ピロリジ
ン - 2 - カルボキサミド

シス - 4 - ヒドロキシ - D - プロリンアミドを用いて、実施例 15 と同様の
 25 方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
 化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ : 1.94 - 2.00 (1H, m), 2.50 - 2.59 (1H, m), 3.11 (3H, s), 3.38 - 3.44 (1H, m), 3.73 - 3.77 (1H, m), 4.23 - 4.28 (1H, m), 4.3

6-4. 42 (1H, m), 7. 12 (2H, d, J=9. 0Hz), 7. 24 (1H, s), 7. 33 (1H, s), 7. 44-7. 47 (1H, m), 7. 89-7. 97 (3H, m), 8. 21-8. 24 (1H, m), 8. 70-8. 72 (1H, m)

5 ESI-MS (m/e) : 494 [M+H]

実施例376

(2R, 4S) - 4-フルオロ-1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-

10 ピロリジン-2-カルボキサミド

実施例375で得られた(2R, 4R)-4-ヒドロキシ-1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-2-カルボキサミドを用いて、実施例356と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

15 ¹HNMR (CD₃OD) δ : 2. 01-2. 21 (1H, m), 2. 54-2. 67 (1H, m), 3. 13 (3H, s), 3. 48 (1H, dd, J=12. 8, 27. 2Hz), 4. 09 (1H, ddd, J=3. 6, 12. 8, 39. 7Hz), 4. 48 (1H, dd, J=6. 4, 10. 0Hz), 5. 20-5. 34 (1H, m), 7. 15 (2H, d, J=8. 8Hz), 7. 25 (1H, brs), 7. 41 (1H, brs), 7. 46-7. 49 (1H, m), 7. 92-7. 99 (3H, m), 8. 26 (1H, d, J=8. 0Hz), 8. 73 (1H, d, J=4. 7Hz)

ESI-MS (m/e) : 496 [M+H]

25

実施例377

(2R, 4S) - 4-ヒドロキシ-1-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-
ピロリジン-2-カルボキサミド

トランス-4-ヒドロキシ-D-プロリンアミドを用いて、実施例15と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 2.00–2.07 (1H, m), 2.33–2.39 (1H, m), 3.13 (3H, s), 3.25 (1H, d, $J=10.8\text{ Hz}$), 4.00 (1H, dd, $J=4.1, 10.8\text{ Hz}$), 4.44–4.50 (2H, m), 7.14 (2H, d, $J=9.0\text{ Hz}$), 7.23 (1H, brs), 7.37 (1H, brs), 7.46–7.49 (1H, m), 7.92–7.99 (3H, m), 8.25 (1H, d, $J=8.0\text{ Hz}$), 8.73 (1H, d, $J=4.7\text{ Hz}$)
ESI-MS (m/e): 494 [$M+H$]

実施例378

1-((2*R*, 4*R*)-1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3*H*-ベンズイミダゾール-5-イル)-4-ヒドロキシ-ピロリジン-2-イル)-エタノン
(工程1)

(2*R*, 4*R*)-1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3*H*-ベンズイミダゾール-5-イル)-4-ヒドロキシ-ピロリジン-2-カルボン酸 メトキシ-メチル-アミドの合成

参考例5で得られた(2*R*, 4*R*)-4-ヒドロキシ-ピロリジン-2-カルボン酸 メトキシ-メチルアミドを用いて、実施例369と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

(工程2)

1-((2*R*, 4*R*)-1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3*H*-ベンズイミダゾール-5-イル)-4-ヒドロキシ-ピロリジン-2-イル)-エタノンの製造

(工程1)で得られた(2*R*, 4*R*)-1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3*H*-ベンズイミダゾール-5-イル)-4-ヒドロキシ-ピロリジン-2-カルボン酸 メトキシ-メチル-アミド 20mg のテトラヒドロフラン1ml 溶液に、-78度
 5 にてメチルリチウム(1.0M ジエチルエーテル溶液) 0.360mlを加えた。反応液を-78度にて1時間攪拌した後、0度まで昇温し、1時間攪拌した。反応液に飽和塩化アンモニウム水溶液を加え、酢酸エチルにて抽出し、無水硫酸マグネシウムにて乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー(KieselgelTM 60F₂₅₄, Art 5744
 10 (メルク社製)、クロロホルム/メタノール=10/1)にて精製し、表題化合物を淡黄色固体として得た。

¹HNMR (CD₃OD) δ: 1.24 (3H, t, J=7.4Hz), 1.79-1.88 (1H, m), 2.08 (3H, s), 2.43-2.54 (1H, m), 3.33 (2H, q, J=7.4Hz), 3.46-3.63 (2
 15 H, m), 4.34-4.43 (2H, m), 7.10 (1H, brs), 7.39 (1H, brs), 7.43-7.50 (2H, m), 7.93-7.97 (1H, m), 8.04 (1H, d, J=8.8Hz), 8.23 (1H, d, J=8.0Hz), 8.46 (1H, d, J=2.7Hz), 8.71 (1H, d, J=4.3Hz)
 20 ESI-MS (m/e): 508 [M+H]

実施例379

1-((2*R*, 4*S*)-1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3*H*-ベンズイミダゾール-5-イル)-4-フルオロ-ピロリジン-2-イル)-エタノン
 25

実施例378で得られた1-((2*R*, 4*R*)-1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3*H*-ベンズイミダゾール-5-イル)-4-ヒドロキシ-ピロリジン-2-イル)-

エタノンを用いて、実施例 356 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.31 (3H, t, $J=7.4\text{ Hz}$), 1.80–2.05 (1H, m), 1.96 and 2.02 (total 3H, each s), 2.26–2.60 (1H, m), 3.30–3.43 (2H, m), 3.43–3.66 (1H, m), 3.70–4.04 (1H, m), 4.50–4.64 (1H, m), 5.12–5.37 (1H, m), 6.90–7.56 (4H, m), 7.80–7.91 (1H, m), 7.93–8.02 (1H, m), 8.30–8.68 (3H, m)

ESI-MS (m/e): 510 $[\text{M}+\text{H}]$

実施例 380

1-((2*R*, 4*S*)-1-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-3*H*-ベンズイミダゾール-5-イル)-4-フルオロ-ピロリジン-2-イル)-エタノン

参考例 5 で得られた (2*R*, 4*R*)-4-ヒドロキシーピロリジン-2-カルボン酸 メトキシーメチルアミドを用いて、実施例 370 及び実施例 378 (工程 2) 及び実施例 356 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 1.98–2.20 (1H, m), 2.05 (3H, s), 2.48–2.61 (1H, m), 3.41 (2H, q, $J=7.4\text{ Hz}$), 3.56 (1H, dd, $J=11.9, 24.5\text{ Hz}$), 3.99 (1H, ddd, $J=3.1, 11.9, 39.1\text{ Hz}$), 4.65 (1H, dd, $J=6.6, 10.3\text{ Hz}$), 5.22–5.36 (1H, m), 7.13 (1H, brs), 7.48–7.50 (2H, m), 8.05 (1H, dd, $J=0.6, 8.8\text{ Hz}$), 8.52 (1H, d, $J=2.8\text{ Hz}$), 8.67 (1H, d, $J=2.5\text{ Hz}$), 8.76 (1H, dd, $J=1.4, 2.5\text{ Hz}$), 9.43 (1H, d, $J=1.4\text{ Hz}$)

ESI-MS (m/e) : 511 [M+H]

実施例 381

5 5-(2-フルオロフェノキシ)-2-ピリジン-2-イル-6-(4-メ
タンスルホニルフェノキシ)-1H-ベンズイミダゾール

実施例 14 で得られた 5-フルオロ-4-(4-メタンスルホニルフェノキシ)-2-ニトロフェニルアミン、及び 2-フルオロフェノールを用いて、実施例 196 (工程 4) ~ (工程 6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

10 $^1\text{H NMR}$ (CD_3OD) δ : 3.10 (3H, s), 6.98-7.05 (1H, m), 7.07-7.21 (5H, m), 7.21-7.66 (3H, m), 7.88 (2H, d, $J=9.0\text{ Hz}$), 7.98 (1H, t, $J=7.6\text{ Hz}$), 8.28 (1H, d, $J=8.2\text{ Hz}$), 8.74 (1H, s)

ESI-MS (m/e) : 476 [M+H]

15

実施例 382

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(4-メ
タンスルホニルフェノキシ)-1H-ベンズイミダゾール

20 実施例 381 で得られた 5-(4-メタンスルホニルフェノキシ)-4-(2-フルオロフェノキシ)-ベンゼン-1,2-ジアミンを用いて、実施例 205 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

25 $^1\text{H NMR}$ (CD_3OD) δ : 3.11 (3H, s), 7.00-7.08 (1H, m), 7.08-7.70 (5H, m), 7.11 (2H, d, $J=8.8\text{ Hz}$), 7.90 (2H, d, $J=8.8\text{ Hz}$), 8.71 (1H, s), 8.78 (1H, s), 9.47 (1H, s)

ESI-MS (m/e) : 477 [M+H]

実施例 383

5- (2, 3-ジフルオロフェノキシ) -2-ピリジン-2-イル-6-
(6-メタンスルホニル-ピリジン-3-イルオキシ) -1H-ベンズイミダ
ゾール

2, 3-ジフルオロフェノールを用いて、実施例196 (工程4) ~ (工程
5 6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を淡黄色固体として得た。

1HNMR (CD₃OD) δ : 3.20 (3H, s), 6.79-6.83 (1
H, m), 6.98-7.12 (2H, m), 7.17-7.80 (4H,
m), 7.98-8.05 (2H, m), 8.27-8.35 (1H, m),
10 8.39 (1H, d, J=2.7 Hz), 8.64-8.79 (1H, m)
ESI-MS (m/e) : 495 [M+H]

実施例384

5- (2, 4-ジフルオロフェノキシ) -2-ピリジン-2-イル-6-
15 (6-メタンスルホニル-ピリジン-3-イルオキシ) -1H-ベンズイミダ
ゾール

2, 4-ジフルオロフェノールを用いて、実施例196 (工程4) ~ (工程
6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を淡黄色固体として得た。

20 1HNMR (CD₃OD) δ : 3.21 (3H, s), 6.91-7.41 (4
H, m), 7.47-7.75 (3H, m), 7.98-8.06 (2H,
m), 8.27-8.33 (1H, m), 8.40-8.45 (1H, m),
8.66-8.76 (1H, m)
ESI-MS (m/e) : 495 [M+H]

25

実施例385

5- (2, 5-ジフルオロフェノキシ) -2-ピリジン-2-イル-6-
(6-メタンスルホニル-ピリジン-3-イルオキシ) -1H-ベンズイミダ
ゾール

2, 5-ジフルオロフェノールを用いて、実施例196（工程4）～（工程6）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

1H NMR (CD₃OD) δ : 3.20 (3H, s), 6.85–6.95 (2
5 H, m), 7.24 (1H, td, J=9.6, 5.1 Hz), 7.53 (1
H, s), 7.56 (1H, dd, J=8.6, 2.7 Hz), 7.64 (1
H, dd, J=7.8, 4.7 Hz), 7.81 (1H, s), 8.05 (1
H, d, J=8.6 Hz), 8.10 (1H, t, J=7.8 Hz), 8.3
3 (1H, d, J=7.8 Hz), 8.43 (1H, d, J=2.7 Hz),
10 8.84 (1H, d, J=4.7 Hz)
ESI-MS (m/e): 495 [M+H]

実施例386

5-(2, 6-ジフルオロフェノキシ)-2-ピリジン-2-イル-6-
15 (6-メタンシルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダ
ゾール

2, 6-ジフルオロフェノールを用いて、実施例196（工程4）～（工程6）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

20 1H NMR (CD₃OD) δ : 3.22 (3H, s), 7.09–7.17 (2
H, m), 7.14 (2H, t, J=8.2 Hz), 7.26–7.32 (1
H, m), 7.47–7.52 (1H, m), 7.55 (1H, dd, J=9.
0, 2.3 Hz), 7.98 (1H, t, J=7.8 Hz), 8.07 (1H,
d, J=9.0 Hz), 8.27 (1H, d, J=7.8 Hz), 8.51
25 (1H, d, J=2.3 Hz), 8.72–8.74 (1H, m)
ESI-MS (m/e): 495 [M+H]

実施例387

5 - (2, 5-ジフルオロフェノキシ) - 2-ピラジン-2-イル-6-
(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダ
ゾール

実施例385で得られた4 - (2, 5-ジフルオロフェノキシ) - 5 -
5 (6-メタンスルホニル-ピリジン-3-イルオキシ) - ベンゼン-1, 2-
ジアミンを用いて、実施例205と同様の方法、これに準じた方法又はこれら
と常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ : 3. 21 (3H, s), 6. 75 - 6. 92 (2
H, m), 7. 17 - 7. 24 (1H, m), 7. 35 - 7. 85 (2H,
10 m), 7. 52 (1H, dd, J = 8. 6, 2. 7 Hz), 8. 04 (1H,
d, J = 8. 6 Hz), 8. 41 (1H, d, J = 2. 7 Hz), 8. 73
(1H, s), 8. 79 (1H, s), 9. 50 (1H, s)

ESI-MS (m/e) : 496 [M+H]

15 実施例388

5 - (3, 4-ジフルオロフェノキシ) - 2-ピラジン-2-イル-6-
(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダ
ゾール

3, 4-ジフルオロフェノールを用いて、実施例383、および実施例38
20 7と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ : 3. 18 (3H, s), 6. 65 (1H, br
s), 6. 80 (1H, br s), 7. 17 (1H, q, J = 9. 4 Hz),
7. 46 (1H, dd, J = 8. 6, 2. 7 Hz), 7. 49 - 7. 80 (2
25 H, m), 8. 00 (1H, d, J = 8. 6 Hz), 8. 33 (1H, d, J
= 2. 7 Hz), 8. 69 (1H, s), 8. 76 (1H, s), 9. 46
(1H, s)

ESI-MS (m/e) : 496 [M+H]

実施例 389

5 - (3, 5-ジフルオロフェノキシ) - 2-ピラジン-2-イル-6 -
(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダ
ゾール

- 5 3, 5-ジフルオロフェノールを用いて、実施例 388 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

1HNMR (CD₃OD) δ : 3.22 (3H, s), 6.41-6.49 (2H, m), 6.60-6.69 (1H, m), 7.50 (1H, dd, J=8.6, 2.7 Hz), 7.54-7.82 (2H, m), 8.04 (1H, d, J=8.6 Hz), 8.36 (1H, d, J=2.7 Hz), 8.74 (1H, brs), 8.80 (1H, brs), 9.52 (1H, s)
 10 ESI-MS (m/e): 496 [M+H]

15 実施例 390

5 - (2-ジフルオロメトキシピリジン-3-イルオキシ) - 6 - (6-メタ
ンスルホニル-ピリジン-3-イルオキシ) - 2 - (5-メチル-ピラジン-
2-イル) - 1H-ベンズイミダゾール

- 20 実施例 215 で得られた 4 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 5 - (6-メタンスルホニル-ピリジン-3-イルオキシ) - ベンゼン-1, 2-ジアミン、及び 5-メチル-ピラジン-2-カルボン酸を用いて、実施例 38 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

1HNMR (CD₃OD) δ : 2.65 (3H, s), 3.18 (3H, s),
 25 7.15 (1H, dd, J=8.0, 4.9 Hz), 7.32-7.80 (2H, m), 7.40 (1H, d, J=7.4 Hz), 7.45 (1H, dd, J=8.8, 2.7 Hz), 7.46 (1H, t, J=72.6 Hz), 7.93 (1H, dd, J=4.9, 1.4 Hz), 8.01 (1H, dd, J=8.8, 0.6 Hz), 8.35 (1H, dd, J=2.7, 0.6 Hz),

8. 67 (1H, d, J=1. 0 Hz), 9. 32 (1H, d, J=1. 3 Hz)

ESI-MS (m/e) : 541 [M+H]

5 実施例 391

5-フェノキシ-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

(工程1)

10 ピラジン-2-カルボン酸 (5-フルオロ-4-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニル)-アミドの合成

実施例 221 (工程1) で得られた 3-フルオロ-4-(6-メタンスルホニル-ピリジン-3-イルオキシ)-フェニルアミン 7. 5 g のジメチルホルムアミド 75 ml 溶液に、ピラジン-2-カルボン酸 3. 8 g、1-ヒドロキシベンゾトリアゾール 4. 1 g、及び 1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・一塩酸塩 5. 8 g を加え、反応液を室温にて一終夜撹拌した。反応液に水を加え、析出した沈殿物を濾取することにより、粗生成物を 8. 0 g 得た。得られた粗生成物 3. 6 g のトリフルオロ酢酸 35 ml 溶液に、発煙硝酸 0. 44 ml を加え、反応液を室温にて一終夜撹拌した後、溶媒を減圧留去した。残渣に水を加え、析出した沈殿物を濾取することにより、
20 表題化合物を得た。

(工程2)

5-(2, 5-ジフルオロ-フェノキシ)-2-ピラジン-2-イル-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの製造

25 (工程1) で得られたピラジン-2-カルボン酸 (5-フルオロ-4-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニル)-アミド 26 mg の N-メチルピロリジノン 0. 5 ml 溶液に、2, 5-ジフルオロ-フェノール 15 mg、及び炭酸セシウム 28 mg を加え、反応液を 90 度にて 15 分間撹拌した後、反応液に塩化スズ (II) 二水和物 100

mgを加えた。反応液を90度にて1時間攪拌した後、酢酸エチル及び飽和重曹水を加えた。沈殿物を濾去後、溶媒を減圧留去し、残渣を逆相中圧液体クロマトグラフィー〔ODS-AS-360-CC (YMC社製) 移動相：水-アセトニトリル-0.1%トリフルオロ酢酸〕にて精製した。得られたフラク

5 ションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.23 (3H, t, $J=7.2\text{ Hz}$), 3.24-3.44 (2H, m), 6.82-6.92 (2H, m), 7.04-7.18 (1H, m), 7.26-7.38 (3H, m), 7.48-7.56

10 (2H, m), 8.03 (1H, d, $J=8.4\text{ Hz}$), 8.38 (1H, s), 8.74 (1H, s), 8.81 (1H, s), 9.51 (1H, s)
ESI-MS (m/e): 474 [M+H]

実施例392

15 5-(ナフタレン-1-イルオキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例391で得られたピラジン-2-カルボン酸 (5-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロフェニル)-アミド、及びナフタレン-1-オールを用いて、実施例391 (工程

20 2)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.17 (3H, t, $J=7.4\text{ Hz}$), 3.29 (2H, q, $J=7.4\text{ Hz}$), 6.81 (1H, d, $J=7.6\text{ Hz}$), 7.29-7.40 (3H, m), 7.45-7.49 (1H, m), 7.55 (1H, d, $J=7.6\text{ Hz}$), 7.56 (1H, s), 7.72 (1H, d, $J=8.6\text{ Hz}$), 7.75 (1H, s), 7.83 (1H, d, $J=8.2\text{ Hz}$), 7.89 (1H, d, $J=8.6\text{ Hz}$), 8.17 (1H, d, $J=3.0\text{ Hz}$), 8.70 (1H, dd, $J=2.3, 1.2\text{ Hz}$), 8.77 (1H, d, $J=2.3\text{ Hz}$), 9.48 (1H, d, $J=1.2\text{ Hz}$)

ESI-MS (m/e) : 524 [M+H]

実施例 393

5 5-(ナフタレン-2-イルオキシ)-2-ピラジン-2-イル-6-(6-
エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

実施例 391 で得られたピラジン-2-カルボン酸 (5-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロ-フェニル)-アミド、及びナフタレン-2-オールを用いて、実施例 391 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
10 により、表題化合物を褐色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.11 (3H, t, $J=7.6\text{ Hz}$), 3.24 (2H, q, $J=7.6\text{ Hz}$), 7.10 (1H, dd, $J=8.8, 2.5\text{ Hz}$), 7.16 (1H, brs), 7.35-7.46 (3H, m), 7.50 (1H, d, $J=3.1\text{ Hz}$), 7.52 (1H, d, $J=2.5\text{ Hz}$),
15 7.67 (1H, d, $J=8.2\text{ Hz}$), 7.81 (1H, s), 7.83 (1H, s), 7.95 (1H, d, $J=6.3\text{ Hz}$), 8.34 (1H, d, $J=2.3\text{ Hz}$), 8.73 (1H, d, $J=2.7\text{ Hz}$), 8.80 (1H, dd, $J=2.7, 1.6\text{ Hz}$), 9.52 (1H, d, $J=1.6\text{ Hz}$)

ESI-MS (m/e) : 524 [M+H]

20

実施例 394

5-(2-ジフルオロメチル-フェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

25 2-ジフルオロメチル-フェノールを用いて、実施例 221 (工程 3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.21 (3H, t, $J=8.4\text{ Hz}$), 3.37 (2H, q, $J=8.4\text{ Hz}$), 6.72 (1H, t, $J=59.8\text{ Hz}$),

6. 85-6. 90 (1H, m), 7. 17 (1H, t, J=8. 6 Hz),
 7. 39-7. 46 (3H, m), 7. 51-7. 84 (3H, m), 7. 9
 8-8. 05 (2H, m), 8. 31-8. 39 (2H, m), 8. 65-8.
 85 (1H, m)

5 ESI-MS (m/e) : 523 [M+H]

実施例 395

5-(2-カルバモイル-フェノキシ)-2-ピリジン-2-イル-6-
(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダ

10 ザール

実施例 196 で得られた 5-(2-シアノ-フェノキシ)-2-ピリジン-
 2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1
 H-ベンズイミダザールを用いて、実施例 43 と同様の方法、これに準じた方
 法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体とし

15 て得た。

1H NMR (CD₃OD) δ : 1. 25 (3H, t, J=7. 3 Hz), 3. 3
 7 (2H, q, J=7. 3 Hz), 6. 88 (1H, d, J=8. 2 Hz),
 7. 16 (1H, t, J=7. 4 Hz), 7. 40-7. 46 (2H, m),
 7. 51-7. 54 (1H, m), 7. 64 (1H, brs), 7. 70 (1
 20 H, brs), 7. 87 (1H, d, J=7. 8 Hz), 7. 98 (1H, d,
 J=8. 6 Hz), 8. 01 (1H, t, J=8. 6 Hz), 8. 30 (1H,
 d, J=2. 7 Hz), 8. 33 (1H, d, J=7. 8 Hz), 8. 76
 (1H, brs)

ESI-MS (m/e) : 516 [M+H]

25

実施例 396

5-ベンジルオキシ-2-ピリジン-2-イル-6-(6-エタンスルホニ
ル-ピリジン-3-イルオキシ)-1H-ベンズイミダザール

実施例 250 (工程 1) で得られた 4-ベンジルオキシ-3-フルオロアニリン、ピコリン酸、及び 6-エタンスルホニル-ピリジン-3-オールを用いて、実施例 250 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

- 5 $^1\text{H NMR}$ (CDCl_3) δ : 1.26 (3H, t, $J=7.6\text{ Hz}$), 3.35 (2H, q, $J=7.6\text{ Hz}$), 5.07 (2H, s), 7.10–7.13 (2H, m), 7.15 (1H, s), 7.26–7.27 (4H, m), 7.34–7.39 (1H, m), 7.51 (1H \times 1/2, s), 7.64 (1H \times 1/2, s), 7.83–7.86 (1H, m), 7.95–7.96 (1H, m), 8.33–8.35 (1H, m), 8.45–8.46 (1H, m), 8.60–8.63 (1H, m), 10.43–10.46 (1H, m)

ESI-MS (m/e): 487 $[\text{M}+\text{H}]$

15 実施例 397

5-(2-メタンスルホニル-6-フルオロフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

(工程 1)

- 20 5-ヒドロキシ-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールの合成

- 25 実施例 396 で得られた 5-ベンジルオキシ-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例 251 (工程 1) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡緑色固体として得た。

(工程 2)

5-(2-メタンスルホニル-6-フルオロフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1

H-ベンズイミダゾールの製造

- (工程1) で得られた5-ヒドロキシ-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール、及び1,2-ジフルオロ-3-メタンスルホニル-ベンゼンを用いて、
- 5 実施例251と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡緑色固体として得た。

- 1H NMR (CD₃OD) δ : 1.25 (3H, t, J=7.4 Hz), 2.97 (3H, s), 3.41 (2H, q, J=7.4 Hz), 7.11 (1H, s), 7.50-7.57 (2H, m), 7.61-7.70 (2H, m),
- 10 7.70 (1H, s), 7.87 (1H, d, J=8.0 Hz), 7.99 (1H, t, J=8.0 Hz), 8.10 (1H, d, J=8.6 Hz), 8.27 (1H, d, J=7.0 Hz), 8.57 (1H, d, J=2.7 Hz), 8.74 (1H, d, J=4.3 Hz)

ESI-MS (m/e): 569 [M+H]

15

実施例398

5-(2-フルオロ-6-シアノフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 20 実施例397で得られた5-ヒドロキシ-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール、及び1,2-ジフルオロ-3-シアノベンゼンを用いて、実施例251と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡緑色固体として得た。

- 25 1H NMR (CD₃OD) δ : 1.26 (3H, t, J=7.4 Hz), 3.39 (2H, q, J=7.4 Hz), 7.27-7.43 (1H, m), 7.40 (1H, td, J=8.0, 4.6 Hz), 7.49-7.55 (2H, m), 7.56-7.76 (3H, m), 7.99 (1H, t, J=7.6 Hz), 8.06 (1H, d, J=9.0 Hz), 8.30 (1H, d, J=7.

6 Hz), 8.46 (1H, d, J=2.7 Hz), 8.75 (1H, d, J=4.3 Hz)

ESI-MS (m/e) : 516 [M+H]

5 実施例 399

5-(2-フルオロ-6-カルバモイル-フェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

10 実施例 397 で得られた 5-(2-フルオロ-6-シアノ-フェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

1H NMR (CD₃OD) δ : 1.25 (3H, t, J=7.4 Hz), 3.40 (2H, q, J=7.4 Hz), 7.00-7.18 (1H, m), 7.34-7.43 (2H, m), 7.49 (1H, brs), 7.54-7.56 (2H, m), 7.66 (1H, brs), 7.97 (1H, t, J=8.0 Hz), 8.07 (1H, d, J=8.6 Hz), 8.20-8.30 (1H, m), 8.53 (1H, d, J=2.7 Hz), 8.70-8.77 (1H, m)

ESI-MS (m/e) : 534 [M+H]

実施例 400

5-(2-フルオロ-6-シアノ-フェノキシ)-2-ピラジン-2-イル-6-(4-エタンスルホニル-フェノキシ)-1H-ベンズイミダゾール
(工程 1)

3-フルオロ-4-(2-フルオロ-6-シアノ-フェノキシ)-フェニルアミンの合成

実施例 196 (工程 1) で得られた (3-フルオロ-4-ヒドロキシ-フェ

ニル) -カルバミン酸 tert-ブチルエステル、及び1, 2-ジフルオロ-3-シアノーベンゼンを用いて、実施例221 (工程1) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

5 (工程2)

ピラジン-2-カルボン酸 (5-フルオロ-4-(2-フルオロ-6-シアノーフェノキシ)-2-ニトロフェニル)-アミドの合成

(工程1) で得られた5-フルオロ-4-(2-フルオロ-6-シアノーフェノキシ)-フェニルアミン、及びピラジン-2-カルボン酸を用いて、実施例391 (工程1) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

(工程3)

5-(2-フルオロ-6-シアノーフェノキシ)-2-ピラジン-2-イル-6-(4-エタンスルホニルフェノキシ)-1H-ベンズイミダゾールの製造

(工程2) で得られたピラジン-2-カルボン酸 (5-フルオロ-4-(2-フルオロ-6-シアノーフェノキシ)-2-ニトロフェニル)-アミド、及び4-エタンスルホニルフェノールを用いて、実施例391 (工程2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

¹H NMR (CD₃OD) δ : 1.24 (3H, t, J=7.4 Hz), 3.20 (2H, q, J=7.4 Hz), 7.12 (2H, d, J=9.0 Hz), 7.33-7.40 (2H, m), 7.55-7.62 (3H, m), 7.86 (2H, d, J=9.0 Hz), 8.72 (1H, s), 8.78 (1H, s), 9.48 (1H, s)

ESI-MS (m/e): 516 [M+H]

実施例401

5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピラジン-2-イル-6 - (4-エタンスルホニル-フェノキシ) - 1H-ベンズイミダゾール、及び5 - (2-フルオロ-6-イソプロピルカルバモイル-フェノキシ) - 2-ピラジン-2-イル-6 - (4-エタンスルホニル-フェノキシ) - 1H-ベンズイミダゾール

5 シ) - 1H-ベンズイミダゾール

実施例400で得られた5 - (2-フルオロ-6-シアノ-フェノキシ) - 2-ピラジン-2-イル-6 - (4-エタンスルホニル-フェノキシ) - 1H-ベンズイミダゾールを用いて、実施例43と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をそれぞれ褐色

10 固体、及び淡黄色固体として得た。

5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピラジン-2-イル-6 - (4-エタンスルホニル-フェノキシ) - 1H-ベンズイミダゾール

1HNMR (CD₃OD) δ : 1.25 (3H, t, J=7.4Hz), 3.2
15 2 (2H, q, J=7.4Hz), 7.00-7.34 (1H, m), 7.2
3 (2H, d, J=8.8Hz), 7.34-7.70 (4H, m), 7.9
1 (2H, d, J=8.8Hz), 8.71 (1H, s), 8.77 (1H,
s), 9.46 (1H, s)

ESI-MS (m/e) : 534 [M+H]

20 5 - (2-フルオロ-6-イソプロピルカルバモイル-フェノキシ) - 2-ピラジン-2-イル-6 - (4-エタンスルホニル-フェノキシ) - 1H-ベンズイミダゾール

1HNMR (CDCl₃) δ : 1.10 (6H, d, J=9.6Hz), 1.2
4 (3H, t, J=7.4Hz), 3.01-3.11 (2H, m), 4.0
25 6-4.16 (1H, m), 6.80-7.87 (9H, m), 8.52-8.
60 (2H, m), 9.51-9.54 (1H, m), 10.78-10.8
0 (1H, m)

ESI-MS (m/e) : 576 [M+H]

実施例 402

5-(2-フルオロ-6-シアノ-フェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 5 実施例 400 (工程 2) で得られたピラジン-2-カルボン酸 (5-フルオロ-4-(2-シアノ-6-フルオロ-フェノキシ)-2-ニトロ-フェニル)-アミド、及び 6-エタンスルホニル-ピリジン-3-オールを用いて、実施例 400 (工程 3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。
- 10 ¹H NMR (DMSO-d₆) δ: 1.10 (3H, t, J=7.4 Hz), 3.27-3.36 (2H, m), 7.22-7.35 (1H, m), 7.38-7.50 (2H, m), 7.72-7.77 (3H, m), 7.98 (1H, d, J=9.0 Hz), 8.50 (1H, d, J=2.7 Hz), 8.76 (1H, s), 8.79 (1H, s), 9.45 (1H, s).
- 15 ESI-MS (m/e): 517 [M+H]

実施例 403

5-(2-フルオロ-6-カルバモイル-フェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール、及び 5-(2-フルオロ-6-イソプロピルカルバモイル-フェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 20 実施例 402 で得られた 5-(2-フルオロ-6-シアノ-フェノキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピラジン-2-イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール

1HNMR (CD₃OD) δ : 1. 27 (3H, t, J=7. 4Hz), 3. 4
5 3 (2H, q, J=7. 4Hz), 7. 08-7. 11 (1H, m), 7. 3
8-7. 46 (2H, m), 7. 46-7. 80 (3H, m), 8. 10 (1
H, d, J=4. 7Hz), 8. 55 (1H, d, J=2. 7Hz), 8. 7
1 (1H, s), 8. 78 (1H, s), 9. 47 (1H, s)

ESI-MS (m/e) : 535 [M+H]

10 5 - (2-フルオロ-6-イソプロピルカルバモイル-フェノキシ) - 2-ピ
ラジン-2-イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキ
シ) - 1H-ベンズイミダゾール

1HNMR (CD₃OD) δ 1. 08 (6H, d, J=6. 6Hz), 1. 25
(3H, t, J=7. 4Hz), 3. 40 (2H, q, J=7. 4Hz), 3.
15 94-4. 02 (1H, m), 7. 10 (1H, s), 7. 36-7. 46
(3H, m), 7. 59 (1H, d, J=9. 0Hz), 7. 74 (1H,
s), 8. 08 (1H, d, J=9. 0Hz), 8. 56 (1H, s), 8.
75 (1H, s), 8. 80 (1H, s), 9. 44 (1H, s)

ESI-MS (m/e) : 577 [M+H]

20

実施例404

5 - (2-フルオロ-6 - (テトラゾール-5-イル) - フェノキシ) - 2-
ピラジン-2-イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキ
シ) - 1H-ベンズイミダゾール

25 実施例402で得られた5 - (2-フルオロ-6-シアノ-フェノキシ) -
2-ピラジン-2-イル-6 - (6-エタンスルホニル-ピリジン-3-イル
オキシ) - 1H-ベンズイミダゾールを用いて、実施例60と同様の方法、こ
れに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を
無色固体として得た。

1HNMR (CD₃OD) δ : 1.27 (3H, t, J=7.4Hz), 3.39 (2H, q, J=7.4Hz), 7.37-7.46 (4H, m), 7.60 (1H, s), 7.84 (1H, d, J=5.9Hz), 7.94 (1H, d, J=9.0Hz), 8.32 (1H, d, J=2.0Hz), 8.71 (1H, s), 8.77 (1H, s), 9.47 (1H, s)
ESI-MS (m/e): 560 [M+H]

実施例405

5-(2-メチルスルファニルフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニルピリジン-3-イルオキシ)-1H-ベンズイミダゾール

2-メチルスルファニルフェノールを用いて、実施例221(工程3)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

1HNMR (CDCl₃) δ : 1.28 (3H, t, J=7.4Hz), 3.38 (2H, q, J=7.4Hz), 6.78 (1H, ddd, J=7.6, 7.6, 1.5Hz), 7.03-7.12 (2H, m), 7.08 (1/2H, s), 7.16 (1H, d, J=7.6Hz), 7.30 (1H, dd, J=8.7, 2.5Hz), 7.36 (1/2H, s), 7.37-7.41 (1H, m), 7.47 (1/2H, s), 7.72 (1/2H, s), 7.86-7.90 (1H, m), 7.97 (1H, d, J=8.7Hz), 8.38 (1H, d, J=2.5Hz), 8.38-8.41 (1H, m), 8.61-8.63 (1H, m), 11.16 (1/2H, brs), 11.28 (1/2H, brs)
ESI-MS (m/e): 519 [M+H]

実施例406

5-(2-メタンスルフィニルフェノキシ)-2-ピリジン-2-イル-6-(6-エタンスルホニルピリジン-3-イルオキシ)-1H-ベンズイミダゾール

ミダゾール、及び5-(2-メタンスルホニル-フェノキシ)-2-ピリジ
ン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-
1H-ベンズイミダゾール

- 実施例405で得られた5-(2-メチルスルファニル-フェノキシ)-
 5 2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イル
 オキシ)-1H-ベンズイミダゾール46mgのメタノール3ml溶液に、水
 2ml、及びオキソン89mgを加えた後、反応液を室温にて5時間攪拌した。
 溶媒を減圧留去した後、得られた残渣を分取用薄層クロマトグラフィー (K i
 e s e l g e l T M 6 0 F 2 5 4、A r t 5 7 4 4 (メルク社製)、クロロホ
 10 ルム/メタノール=15/1)にて精製し、表題化合物をそれぞれ淡黄色固体
 として得た。

5-(2-メタンスルフィニル-フェノキシ)-2-ピリジン-2-イル-
6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイ
ミダゾール

- 15 ¹H NMR (CDCl₃) δ: 1.30 (3H, t, J=7.6 Hz), 2.5
 9 (3/2H, s), 2.63 (3/2H, s), 3.38 (2H, q, J=
 7.6 Hz), 6.78-6.81 (1H, m), 7.25-7.33 (2H,
 m), 7.35-7.43 (1H, m), 7.08 (1/2H, s), 7.1
 6 (1H, d, J=7.6 Hz), 7.30 (1H, dd, J=8.7, 2.
 20 5 Hz), 7.36 (1/2H, s), 7.37-7.41 (1H, m), 7.
 47 (1/2H, s), 7.72 (1/2H, s), 7.86-7.90 (1
 H, m), 7.97 (1H, d, J=8.7 Hz), 8.38 (1H, d, J
 =2.5 Hz), 8.38-8.41 (1H, m), 8.61-8.63 (1
 H, m), 11.16 (1/2H, br s), 11.28 (1/2H, br
 25 s)

E S I - M S (m/e) : 535 [M+H]

5-(2-メタンスルホニル-フェノキシ)-2-ピリジン-2-イル-6-
(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダ
ゾール

1HNMR (CDCl₃) δ : 1.29 (3H, t, J=7.4Hz), 2.95 (3/2H, s), 3.02 (3/2H, s), 3.36 (2H, q, J=7.4Hz), 6.92-6.97 (1H, d), 7.20-7.27 (1H, m), 7.31-7.35 (3/2H, m), 7.41-7.45 (3/2H, m), 7.51-7.57 (1H, m), 7.65 (1/2H, s), 7.72 (1/2H, s), 7.87-7.92 (1H, m), 7.97-8.04 (2H, m), 8.34-8.42 (2H, m), 8.65-8.67 (1H, m), 10.72 (1H, brs)
 ESI-MS (m/e): 551 [M+H]

10

実施例407

5-(2-ブロモピリジン-3-イルオキシ)-2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダゾール

- 15 実施例391で得られたピラジン-2-カルボン酸 (5-フルオロ-4-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ニトロフェニル)-アミド、及び2-ブロモ-ピリジン-3-オールを用いて、実施例391と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。
- 20 1HNMR (CDCl₃) δ : 1.30 (3H, t, J=7.4Hz), 3.39 (2H, q, J=7.4Hz), 7.03 (1H, dd, J=8.0, 1.6z), 7.19-7.22 (1H, m), 7.28-7.32 (1H, m), 7.34 (1/2H, brs), 7.51 (1/2H, brs), 7.62 (1/2H, brs), 7.93 (1/2H, brs), 8.00 (1H, d, J=8.6Hz), 8.14 (1H, brs), 8.31-8.32 (1H, m), 8.62 (1H, brs), 8.70 (1H, d, J=2.4Hz), 9.64 (1H, brs), 10.91 (1/2H, brs), 10.98 (1/2H, brs)
 25 ESI-MS (m/e): 553 [M+H]

実施例 408

5-(2-ビニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-
6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイ
 5 ミダゾール

2-ビニル-ピリジン-3-オールを用いて、実施例 407 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

1HNMR (CDCl₃) δ: 1.27 (3H, t, J=7.5 Hz), 3.3
 10 7 (2H, q, J=7.5 Hz), 5.34 (1H, dd, J=10.9, 1.
 9 Hz), 6.30 (1H, dd, J=17.4, 1.9 Hz), 6.72
 (1H, dd, J=17.4, 10.9 Hz), 7.09 (1H, dd, J=
 8.2, 1.5 Hz), 7.12 (1H, dd, J=8.2, 4.3 Hz),
 7.27 (1H, dd, J=8.7, 2.9 Hz), 8.00 (1H, d, J
 15 =8.7 Hz), 8.31 (1H, d, J=2.9 Hz), 8.33 (1H,
 dd, J=4.3, 1.5 Hz), 8.61 (1H, dd, J=2.6, 1.
 6 Hz), 8.69 (1H, d, J=2.6 Hz), 10.60 (1/2H,
 brs), 10.68 (1/2H, brs)
 ESI-MS (m/e): 501 [M+H]

20

実施例 409

5-(2-シクロプロピル-ピリジン-3-イルオキシ)-2-ピラジン-
2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-1
H-ベンズイミダゾール

25 2-シクロプロピル-ピリジン-3-オールを用いて、実施例 407 と同様の
 の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表
 題化合物を淡黄色固体として得た。

1HNMR (CDCl₃) δ: 0.77-1.02 (2H, m), 1.24-1.
 31 (2H, m), 1.29 (3H, t, J=7.4 Hz), 3.37 (2H,

q, $J=7.4\text{ Hz}$), 6.96 (2/5H, dd, $J=8.2, 4.6\text{ Hz}$), 6.98 (3/5H, dd, $J=8.2, 4.6\text{ Hz}$), 7.03 (2/5H, dd, $J=8.2, 1.5\text{ Hz}$), 7.04 (3/5H, dd, $J=8.2, 1.5\text{ Hz}$), 7.16 (1/2H, s), 7.33 (1H, dd, $J=8.8, 3.0\text{ Hz}$), 7.48 (1/2H, s), 7.53 (1/2H, s), 7.78 (1/2H, s), 8.00 (1H, d, $J=8.8\text{ Hz}$), 8.20 (2/5H, dd, $J=4.6, 1.5\text{ Hz}$), 8.22 (3/5H, dd, $J=4.6, 1.5\text{ Hz}$), 8.39 (2/5H, d, $J=3.0\text{ Hz}$), 8.40 (3/5H, d, $J=3.0\text{ Hz}$), 8.59–8.62 (1H, m), 8.68–8.70 (1H, m), 9.62–9.64 (1H, m), 10.60 (3/5H, brs), 10.66 (2/5H, brs)
 ESI-MS (m/e): 515 [M+H]

実施例 410

15 5-(2-ジフルオロメトキシピリジン-3-イルオキシ)-2-ピリジン-2-イル-6-(4-ジメチルサルファモイル-フェノキシ)-1H-ベンズイミダゾール

4-(N, N-ジメチルアミノスルホニル)-フェノール、及び2-ジフルオロメトキシ-ピリジン-3-オールを順次用いて、実施例 221 (工程1) ~ (工程3) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

1HNMR (CD_3OD) δ : 2.66 (6H, s), 7.05 (2H, d, $J=8.6\text{ Hz}$), 7.10–7.19 (1H, m), 7.32–7.62 (4H, m), 7.49 (1H, t, $J=72.8\text{ Hz}$), 7.71 (2H, d, $J=8.6\text{ Hz}$), 7.91 (1H, d, $J=4.1\text{ Hz}$), 8.01 (1H, t, $J=7.8\text{ Hz}$), 8.32 (1H, d, $J=7.6\text{ Hz}$), 8.77 (1H, s)

ESI-MS (m/e): 554 [M+H]

実施例 411

5 - (2-ジフルオロメトキシピリジン-3-イルオキシ) - 6 - (3-クロ
ロ-4-メタンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1H-
ベンズイミダゾール

- 5 4-メタンスルホニル-3-クロロ-フェノール、及び2-ジフルオロメト
キシ-ピリジン-3-オールを順次用いて、実施例221（工程1）～（工程
3）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を淡黄色固体として得た。

- 1HNMR (CD₃OD) δ : 3.25 (3H, s), 6.98 (1H, dd,
10 J=8.6, 2.3 Hz), 7.09 (1H, d, J=2.3 Hz), 7.1
5 (1H, dd, J=7.8, 4.9 Hz), 7.35-7.46 (2H,
m), 7.46-7.74 (3H, m), 7.48 (1H, t, J=74.0
Hz), 7.91-7.94 (1H, m), 8.02 (1H, d, J=8.6
Hz), 8.32 (1H, d, J=7.8 Hz), 8.75-8.77 (1H,
15 m)
ESI-MS (m/e): 552 [M-H]

実施例 412

- 5 - (2-フルオロ-フェノキシ) - 2-ピラジン-2-イル-6 - (4-
20 (N-ヒドロキシカルバムイミドイル) - フェノキシ) - 1H-ベンズイミダ
ゾール

- 実施例252で得られた5-(2-フルオロ-フェノキシ)-2-ピラジ
ン-2-イル-6-(6-シアノ-ピリジン-3-イルオキシ)-1H-ベン
ズイミダゾール6.0mgのエタノール0.5ml溶液に、ヒドロキシアミン
25 (50%水溶液) 0.5ml加え、反応液を室温にて3時間攪拌した後、溶媒
を減圧留去することにより、表題化合物を淡黄色固体として得た。

1HNMR (CD₃OD) δ : 7.01-7.04 (1H, m), 7.10-7.
22 (3H, m), 7.29-7.35 (2H, m), 7.60 (1H, s),
7.82 (1H, d, J=9.0 Hz), 8.24 (1H, d, J=2.3 H

z), 8.70 (1H, d, J=1.6 Hz), 8.77 (1H, d, J=1.6 Hz), 9.48 (1H, s)

ESI-MS (m/e) : 458 [M+H]

5 実施例 413

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-(5-メチル-[1,2,4]オキサジアゾール)-3-イルオキシ)-1H-ベンズイミダゾール

実施例 412 で得られた 5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(4-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-1H-ベンズイミダゾール 3.6 mg の無水酢酸 1 ml 溶液を、60 度にて一終夜攪拌した。溶媒を減圧留去し、残渣を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相 : 水-アセトニトリル-0.1%トリフルオロ酢酸] にて精製した。得られたフラクションの溶媒を酢酸エチルにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、表題化合物を無色固体として得た。

¹H NMR (CD₃OD) δ : 2.69 (3H, s), 7.00-7.40 (5H, m), 7.48 (1H, dd, J=7.8, 2.3 Hz), 7.52-7.85 (1H, m), 8.10 (1H, d, J=7.8 Hz), 8.37 (1H, d, J=2.3 Hz), 8.71 (1H, s), 8.78 (1H, s), 9.48 (1H, s)

ESI-MS (m/e) : 482 [M+H]

実施例 414

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-(5-トリフルオロメチル-[1,2,4]オキサジアゾール)-3-イルオキシ)-1H-ベンズイミダゾール

実施例 412 で得られた 5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(4-(N-ヒドロキシカルバムイミドイル)-フェノキシ)-1H-ベンズイミダゾール

シ) -1H-ベンズイミダゾール2. 0mgの無水トリフルオロ酢酸1ml溶液を、60度にて1時間攪拌した。溶媒を減圧留去し、残渣を分取用薄層クロマトグラフィー (Kieselgel TM60F254、Art 5744 (メルク社製)、クロロホルム/メタノール=15/1) にて精製し、表題化合物
5 を無色固体として得た。

¹H NMR (CD₃OD) δ: 7.00-7.50 (5H, m), 7.55 (1H, dd, J=7.8 Hz, 2.3 Hz), 7.60-7.80 (1H, m), 8.22 (1H, d, J=7.8 Hz), 8.45 (1H, d, J=2.3 Hz), 8.73 (1H, s), 8.80 (1H, s), 9.50 (1H, s)

10 ESI-MS (m/e): 536 [M+H]

実施例 415

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(イミダゾ
ゾ[1, 2-a]ピリジン-6-イルオキシ)-1H-ベンズイミダゾール

15 (工程1)

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-ニトロピリジン-3-イルオキシ)-1H-ベンズイミダゾールの合成

2-ニトロ-5-ピリジンを用いて、実施例251(工程2)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
20 を得た。

(工程2)

5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(イミダゾ[1, 2-a]ピリジン-6-イルオキシ)-1H-ベンズイミダゾールの製造

25 (工程1)で得られた5-(2-フルオロフェノキシ)-2-ピラジン-2-イル-6-(6-ニトロピリジン-3-イルオキシ)-1H-ベンズイミダゾール12mgのメタノール0.5ml溶液に、展開ラネーニッケル触媒を加え、反応液を水素雰囲気下、1時間攪拌した。触媒を濾去後、溶媒を減圧留去した。得られた残渣のエタノール0.3ml溶液に、クロロアセトアルデ

ヒド (40%水溶液) 0.02mlを加えた後、反応液を室温にて一終夜攪拌した。溶媒を減圧留去した後、残渣を分取用薄層クロマトグラフィー (Kiesel gel TM60F254、Art 5744 (メルク社製)、クロロホルム/メタノール=15/1) にて精製し、表題化合物を淡黄色固体として得た。

5 $^1\text{H NMR}$ (CDCl_3) δ : 1.25 (3H, t, $J=7.0\text{ Hz}$), 3.73 (2H, q, $J=7.0\text{ Hz}$), 7.00–7.22 (6H, m), 7.31–7.65 (4H, m), 7.82 (1/2H, s), 7.88 (1/2H, s), 8.57 (1H, dd, $J=2.5, 1.5\text{ Hz}$), 8.64 (1H, s), 9.59 (1H, s), 10.57 (1/2H, brs), 10.97
10 (1/2H, brs)

ESI-MS (m/e): 439 $[\text{M}+\text{H}]$

実施例 416

5 5-(ピリジン-2-イルスルファニル)-2-ピラジン-2-イル-6-
15 (6-エタンスルホニル-ピリジン-3-イルオキシ)-1H-ベンズイミダ
ゾール

ピリジン-2-チオールを用いて、実施例 391 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

20 $^1\text{H NMR}$ (CD_3OD) δ : 1.23 (3H, t, $J=7.4\text{ Hz}$), 3.36 (2H, q, $J=7.4\text{ Hz}$), 7.07 (1H, d, $J=8.2\text{ Hz}$), 7.11 (1H, dd, $J=7.4, 4.9\text{ Hz}$), 7.41 (1H, d, $J=7.6\text{ Hz}$), 7.58–7.80 (1H, m), 7.60 (1H, td, $J=7.6, 1.8\text{ Hz}$), 7.95 (1H, dd, $J=8.6, 0.6\text{ Hz}$),
25 z), 8.00–8.25 (1H, m), 8.28 (1H, dd, $J=5.1, 1.0\text{ Hz}$), 8.33 (1H, d, $J=0.6\text{ Hz}$), 8.75 (1H, d, $J=2.5\text{ Hz}$), 8.82 (1H, dd, $J=2.5, 1.5\text{ Hz}$), 9.53 (1H, d, $J=1.5\text{ Hz}$)

ESI-MS (m/e): 491 $[\text{M}+\text{H}]$

実施例 417

5 - (3 - シアノーピリジン - 2 - イルスルファニル) - 2 - ピラジン - 2 -
イル - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベ

5. ンズイミダゾール

3 - シアノーピリジン - 2 - チオールを用いて、実施例 391 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

1HNMR (CDCl₃) δ : 1.29 (3H, t, J=7.4 Hz), 3.3
 10 6 (2H, q, J=7.4 Hz), 7.08 (1H, dd, J=7.8, 4.9 Hz), 7.35 (1H, dd, J=8.6, 2.8 Hz), 7.35 a
 nd 7.65 (total 1H, each s), 7.80 (1H, dd, J=7.8, 1.8 Hz), 7.93 (1H, d, J=8.4 Hz), 7.9
 5 and 8.22 (total 1H, each s), 8.36 (2H,
 15 d, J=2.5 Hz), 8.63 (1H, s), 8.71 (1H, s), 9.
 65 (1H, d, J=1.4 Hz)

ESI-MS (m/e): 516 [M+H]

実施例 418

20 5 - (2 - クロロフェニル - スルファニル) - 2 - ピリジン - 2 - イル - 6 -
(6 - メタンスルホニル - ピリジン - 3 - イルオキシ) - 1H - ベンズイミダ
ゾール

25 2 - グローチオフェノールを用いて、実施例 196 (工程 4) ~ (工程 6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

1HNMR (CD₃OD) δ : 3.20 (3H, s), 7.03 - 7.10 (1
 H, m), 7.13 - 7.20 (2H, m), 7.34 - 7.39 (2H,
 m), 7.50 - 7.86 (3H, m), 7.94 (1H, d, J=8.6 H

z), 8.01 (1H, t, J=7.8 Hz), 8.29-8.35 (2H, m), 8.77 (1H, d, J=4.7 Hz)

ESI-MS (m/e): 509 [M+H]

実施例 419

5 4-(2-シアノフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-シアノフェノール、及び6-エタンスルホニルピリジン-3-オールを順次用いて、実施例274と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

10 ¹H NMR (CD₃OD) δ: 1.25 (3H, t, J=7.4 Hz), 3.40 (2H, q, J=7.4 Hz), 6.78 (1H, s), 7.12 (1H, d, J=8.6 Hz), 7.29-7.31 (2H, m), 7.50-7.51 (1H, m), 7.63-7.65 (2H, m), 7.82 (1H, d, J=7.4 Hz), 7.95-7.97 (1H, m), 8.08 (1H, d, J=8.6 Hz),
15 = 8.6 Hz), 8.32 (1H, d, J=8.2 Hz), 8.55 (1H, d, J=2.7 Hz), 8.75 (1H, d, J=4.3 Hz)

ESI-MS (m/e): 498 [M+H]

実施例 420

20 4-(2-シアノフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例419で得られた3-(2-シアノフェノキシ)-5-(6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンを用いて、実施例205と同様の方法、これに準じた方法又はこれらと常法とを
25 組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CD₃OD) δ: 1.27 (3H, t, J=8.0 Hz), 3.42 (2H, q, J=8.0 Hz), 6.79-6.84 (1H, m), 7.14-7.17 (1H, m), 7.31-7.35 (1H, m), 7.61-7.68 (2H, m), 7.80-7.85 (2H, m), 8.08 (1H, d,

$J = 8.4 \text{ Hz}$), $8.54 - 8.59$ (1H, m), $8.70 - 8.73$ (1H, m), $8.77 - 8.79$ (1H, m), $9.48 - 9.50$ (1H, m)

ESI-MS (m/e): 499 [M+H]

5

実施例 421

4-(2-シアノフェノキシ)-6-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例 286 で得られた 3-(2-シアノフェノキシ)-5-(6-メタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンを用いて、実施例 205 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.24 (3H, s), 6.80-6.83 (1H, m), 7.72 (1H, d, $J = 8.6 \text{ Hz}$), 7.30-7.50 (2H, m), 7.60-7.80 (2H, m), 7.88 (1H, d, $J = 7.8 \text{ Hz}$), 8.11 (1H, d, $J = 9.0 \text{ Hz}$), 8.56 (1H, s), 8.73 (1H, s), 8.79 (1H, s), 9.50 (1H, s)

ESI-MS (m/e): 485 [M+H]

20 実施例 422

4-(2,3-ジフルオロフェノキシ)-6-(6-メタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

2,3-ジフルオロフェノール、及び 6-メタンスルホニルピリジン-3-オールを順次用いて、実施例 274 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.23 (3H, s), 6.70 (1H, d, $J = 2.3 \text{ Hz}$), 7.12-7.25 (3H, m), 7.29 (1H, d, $J = 2.3 \text{ Hz}$), 7.60-7.65 (2H, m), 8.07-8.10 (2

H, m), 8.39 (1H, d, J=7.9 Hz), 8.50 (1H, d, J=3.4 Hz), 8.83-8.85 (1H, m)

ESI-MS (m/e) : 495 [M+H]

5 実施例 423

4-(2,3-ジフルオロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

10 実施例 285 で得られた 3-(2,3-ジフルオロフェノキシ)-5-(6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンを用いて、実施例 204 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹H NMR (CD₃OD) δ : 1.25 (3H, t, J=7.6 Hz), 3.40 (2H, q, J=7.6 Hz), 6.71 (1H, d, J=2.0 Hz),
15 7.12-7.26 (3H, m), 7.30 (1H, d, J=2.0 Hz), 7.60-7.68 (2H, m), 8.06-8.13 (2H, m), 8.40 (1H, d, J=7.4 Hz), 8.52 (1H, d, J=2.7 Hz), 8.86 (1H, d, J=5.1 Hz)

ESI-MS (m/e) : 509 [M+H]

20

実施例 424

4-(2,5-ジフルオロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

25 2,5-ジフルオロフェノール、及び 6-エタンスルホニルピリジン-3-オールを順次用いて、実施例 278 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CD₃OD) δ : 1.25 (3H, t, J=8.2 Hz), 3.41 (2H, q, J=8.2 Hz), 6.59 (1H, s), 6.99-7.0

5 (1H, m), 7.06–7.14 (1H, m), 7.22 (1H, br s), 7.34 (1H, td, J=9.8, 4.9 Hz), 7.61 (1H, dd, J=8.6, 4.3 Hz), 8.07 (1H, d, J=8.6 Hz), 8.52 (1H, d, J=4.3 Hz), 8.72 (1H, d, J=1.2 Hz), 8.79 (1H, s), 9.54 (1H, d, J=1.2 Hz)
 ESI-MS (m/e) : 510 [M+H]

実施例 425

4-(2, 5-ジフルオロフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 424 で得られた 3-(2, 5-ジフルオロフェノキシ)-5-(6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミンを用いて、実施例 204 (工程 2) と同様の方法、これに準じた方法
 又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CD₃OD) δ : 1.25 (3H, t, J=7.5 Hz), 3.40 (2H, q, J=7.5 Hz), 6.55 (1H, s), 6.96–7.05 (1H, m), 7.05–7.14 (1H, m), 7.21 (1H, s), 7.28–7.38 (1H, m), 7.50–7.56 (1H, m), 7.56–7.63 (1H, m), 7.97–8.03 (1H, m), 8.07 (1H, d, J=8.2 Hz), 8.38 (1H, d, J=7.0 Hz), 8.51 (1H, s), 8.76 (1H, s)

ESI-MS (m/e) : 509 [M+H]

実施例 426

4-(2, 6-ジフルオロフェノキシ)-6-(4-エタンスルホニルフェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

2, 6-ジフルオロフェノール、及び 4-エタンスルホニルフェノール

を順次用いて、実施例 278 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.26 (3H, t, $J=7.4\text{ Hz}$), 3.21 (2H, q, $J=7.4\text{ Hz}$), 6.37 (1H, brs), 7.13–7.25 (5H, m), 7.34–7.39 (1H, m), 7.89 (2H, d, $J=8.8\text{ Hz}$), 8.78 (1H, d, $J=2.7\text{ Hz}$), 8.84 (1H, dd, $J=1.6, 2.7\text{ Hz}$), 9.56 (1H, d, $J=1.6\text{ Hz}$)
ESI-MS (m/e): 509 [M+H]

10 実施例 427

4-(2,6-ジフルオロフェノキシ)-6-(4-エタンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 426 で得られた 3-(2,6-ジフルオロフェノキシ)-5-(4-エタンスルホニルフェノキシ)-ベンゼン-1,2-ジアミンを用いて、実施例 204 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.21 (2H, q, $J=7.4\text{ Hz}$), 6.23 (1H, brs), 7.08 (1H, brs), 7.15–7.22 (4H, m), 7.28–7.38 (1H, m), 7.51 (1H, t, $J=5.9\text{ Hz}$), 7.87 (2H, d, $J=9.0\text{ Hz}$), 8.00 (1H, t, $J=7.4\text{ Hz}$), 8.41 (1H, d, $J=7.4\text{ Hz}$), 8.76 (1H, brs)
ESI-MS (m/e): 508 [M+H]

25 実施例 428

4-(2-ジフルオロメチルフェノキシ)-6-(6-エタンスルホニルピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2-ジフルオロメチルフェノール、及び 6-エタンスルホニルピリジ

ン-3-オールを順次用いて、実施例274と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色固体として得た。

¹H NMR (CD₃OD) δ : 1.24 (3H, t, J=7.4 Hz), 3.3
 5 9 (2H, q, J=7.4 Hz), 6.50 (1H, s), 7.15 (1H,
 d, J=7.4 Hz), 7.22 (1H, t, J=55.5 Hz), 7.34
 (1H, t, J=7.4 Hz), 7.49-7.62 (4H, m), 7.74
 (1H, d, J=7.4 Hz), 7.98 (1H, t, J=7.4 Hz), 8.
 05 (1H, d, J=8.6 Hz), 8.37 (1H, d, J=7.4 Hz),
 10 8.49 (1H, d, J=2.3 Hz), 8.74-8.77 (1H, m)
 ESI-MS (m/e) : 523 [M+H]

実施例429

4-(2-ジフルオロメチルフェノキシ)-6-(6-エタンスルホニル-
 15 ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダ
ゾール

実施例428で得られた3-(2-ジフルオロメチルフェノキシ)-5-
 (6-エタンスルホニルピリジン-3-イルオキシ)-ベンゼン-1,2-
 ジアミンを用いて、実施例205と同様の方法、これに準じた方法又はこれら
 20 と常法とを組み合わせることにより、表題化合物を黄色固体として得た。

¹H NMR (CD₃OD) δ : 1.25 (3H, t, J=7.8 Hz), 3.4
 0 (2H, q, J=7.8 Hz), 6.54 (1H, s), 7.17 (1H,
 d, J=7.4 Hz), 7.21 (1H, t, J=55.8 Hz), 7.36
 (1H, t, J=7.4 Hz), 7.50-7.65 (2H, m), 7.75
 25 (1H, d, J=7.4 Hz), 8.06 (1H, d, J=8.6 Hz), 8.
 51 (1H, d, J=2.7 Hz), 8.72 (1H, s), 8.79 (1H,
 s), 9.54 (1H, s)
 ESI-MS (m/e) : 524 [M+H]

実施例 430

4-(2-ジフルオロメトキシ-ピリジン-3-イルオキシ)-6-(4-エ
タンスルホニル-フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミ
ダゾール

- 5 2-ジフルオロメトキシ-ピリジン-3-オール、及び4-エタンスルホニル-フェノールを順次用いて、実施例274と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- $^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.3\text{ Hz}$), 3.40 (2H, q, $J=7.3\text{ Hz}$), 6.60 (1H, d, $J=2.0\text{ Hz}$),
 10 7.27-7.30 (2H, m), 7.57-7.61 (2H, m), 7.64 (1H, t, $J=7.2.1\text{ Hz}$), 7.73 (1H, dd, $J=7.8, 1.6\text{ Hz}$), 8.05-8.08 (2H, m), 8.10 (1H, dd, $J=4.9, 1.6\text{ Hz}$), 8.37 (1H, d, $J=8.2\text{ Hz}$), 8.51 (1H, d, $J=2.7\text{ Hz}$), 8.81 (1H, d, $J=4.9\text{ Hz}$)
 15 ESI-MS (m/e): 540 [$\text{M}+\text{H}$]

実施例 431

- 4-(1-メチル-2-オキソ-1,2-ジヒドロ-ピリジン-3-イルオキシ)-6-(4-エタンスルホニル-フェノキシ)-2-ピラジン-2-イ
ル-1H-ベンズイミダゾール
- 20

- 実施例274(工程1)で得られた3-(1-メチル-2-オキソ-1,2-ジヒドロ-ピリジン-3-イルオキシ)-5-(4-エタンスルホニル-フェノキシ)-ベンゼン-1,2-ジアミンを用いて、実施例205と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
 25 化合物を淡黄色固体として得た。

- $^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.21 (2H, q, $J=7.4\text{ Hz}$), 3.65 (3H, s), 6.38 (1H, t, $J=7.2\text{ Hz}$), 6.44 (1H, s), 7.07 (1H, s), 7.15-7.22 (2H, m), 7.40 (1H, d, $J=7.0\text{ Hz}$), 7.

5 7 (1H, dd, $J=7.0, 1.8$ Hz), 7.84–7.90 (2H, m), 8.70 (1H, s), 8.76 (1H, s), 9.52 (1H, s)

ESI-MS (m/e): 504 [M+H]

5 実施例 432

4-(1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

10 1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-オール、及び
6-エタンスルホニル-ピリジン-3-オールを順次用いて、実施例 274 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡褐色固体として得た。

^1H NMR (CD_3OD) δ : 1.26 (3H, t, $J=7.4$ Hz), 3.40 (2H, q, $J=7.4$ Hz), 3.65 (3H, s), 6.36 (1H, t, $J=6.7$ Hz), 6.46 (1H, s), 7.13 (1H, s), 7.38–7.60 (4H, m), 7.95–8.08 (2H, m), 8.35 (1H, s), 8.49 (1H, s), 8.73 (1H, s)

ESI-MS (m/e): 504 [M+H]

20 実施例 433

4-(1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

25 実施例 432 で得られた 3-(1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキシ)-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1, 2-ジアミンを用いて、実施例 205 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR ($\text{DMSO}-d_6$) δ : 1.13 (3H, t, $J=7.4$ Hz), 3.

4.0 (2H, q, $J=7.4$ Hz), 3.50 (3H, s), 6.24 (1H, t, $J=6.8$ Hz), 6.46 (1H, s), 7.05 (1H, br s), 7.32–7.40 (1H, m), 7.58 (1H, dd, $J=8.8, 2.5$ Hz), 7.74 (1H, dd, $J=6.8, 2.0$ Hz), 8.01 (1H, d, $J=8.6$ Hz), 8.57 (1H, d, $J=2.5$ Hz), 8.79 (1H, d, $J=2.2$ Hz), 8.82 (1H, dd, $J=2.5, 1.5$ Hz), 9.47 (1H, d, $J=1.4$ Hz)

ESI-MS (m/e): 505 [M+H]

10 実施例 434

4-(2-シアノーピリジン-3-イルオキシ)-6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

(工程 1)

5-(4-メタンスルホニルフェノキシ)-2-ニトロ-3-(1-オキシーピリジン-3-イルオキシ)-フェニルアミンの合成

1-オキシーピリジン-3-オール、及び 6-メタンスルホニルピリジン-3-オールを用いて、実施例 67 (工程 1) 及び (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

20 (工程 2)

5-(4-メタンスルホニルフェノキシ)-2-ニトロ-3-(2-シアノーピリジン-3-イルオキシ)-フェニルアミンの合成

5-(4-メタンスルホニルフェノキシ)-2-ニトロ-3-(1-オキシーピリジン-3-イルオキシ)-フェニルアミンを用いて、実施例 218

25 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

(工程 3)

4- (2-シアノーピリジン-3-イルオキシ) -6- (4-メタンスルホ
ニル-フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾールの
製造

5 5- (4-メタンスルホニル-フェノキシ) -2-ニトロ-3- (2-シア
ノーピリジン-3-イルオキシ) -フェニルアミンを用いて、実施例196
 (工程5) 及び204 (工程1) と同様の方法、これに準じた方法又はこれら
 と常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.23 (3H, s), 7.07 (1H, br
s), 7.44 (1H, brs), 7.56-7.69 (4H, m), 8.0
10 2 (1H, t, $J=7.8\text{ Hz}$), 8.09 (1H, d, $J=8.6\text{ Hz}$),
8.29 (1H, d, $J=7.8\text{ Hz}$), 8.46-8.48 (1H, m),
8.55-8.57 (1H, m), 8.78-8.80 (1H, m)
ESI-MS (m/e): 485 $[\text{M}+\text{H}]$

15 実施例435

4- (2-シアノーピリジン-3-イルオキシ) -6- (4-エタンスルホニ
ル-フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール

4-エタンスルホニル-フェノールを用いて、実施例434と同様の方法、
これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
20 を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.25 (3H, t, $J=7.3\text{ Hz}$), 3.2
2 (2H, q, $J=7.3\text{ Hz}$), 6.94 (1H, brs), 7.27 (2
H, d, $J=8.6\text{ Hz}$), 7.33 (1H, brs), 7.49 (2H, d,
 $J=8.6\text{ Hz}$), 7.59-7.62 (1H, m), 7.91-7.98
25 (3H, m), 8.24 (1H, d, $J=8.6\text{ Hz}$), 8.45 (1H, d,
 $J=5.1\text{ Hz}$), 8.74 (1H, d, $J=5.5\text{ Hz}$)
ESI-MS (m/e): 498 $[\text{M}+\text{H}]$

実施例436

4-ベンジルオキシ-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

ベンジルアルコール、及び6-エタンスルホニル-ピリジン-3-オールを
順次用いて、実施例274と同様の方法、これに準じた方法又はこれらと常法
5 とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.6\text{ Hz}$), 3.45 (2H, q, $J=7.6\text{ Hz}$), 5.41 (2H, s), 7.02-7.05 (1H, m), 7.15-7.17 (1H, m), 7.39-7.45 (3H, m), 7.53-7.59 (4H, m), 8.07 (1H, d, $J=8.6\text{ Hz}$), 8.11-8.14 (1H, m), 8.39 (1H, d, $J=7.0\text{ Hz}$), 8.53 (1H, d, $J=2.7\text{ Hz}$), 8.87-8.90 (1H, m)

ESI-MS (m/e): 487 [$M+H$]

15 実施例437

4-ベンジルオキシ-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

実施例436で得られた3-ベンジルオキシ-5-(6-エタンスルホニル-ピリジン-3-イルオキシ)-ベンゼン-1,2-ジアミンを用いて、実施
20 例205と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.27 (3H, t, $J=7.4\text{ Hz}$), 3.42 (2H, q, $J=7.4\text{ Hz}$), 5.38 (2H, s), 6.80 (1H, d, $J=2.0\text{ Hz}$), 7.06 (1H, d, $J=2.0\text{ Hz}$), 7.36-7.42 (3H, m), 7.49 (1H, dd, $J=8.8, 2.9\text{ Hz}$), 7.54 (2H, d, $J=6.7\text{ Hz}$), 8.03 (1H, d, $J=8.8\text{ Hz}$), 8.49 (1H, d, $J=2.7\text{ Hz}$), 8.72 (1H, d, $J=2.7\text{ Hz}$), 8.78-8.80 (1H, m), 9.54-9.56 (1H, m)

ESI-MS (m/e) : 488 [M+H]

実施例 438

4- (2-シアノ-6-フルオロ-フェノキシ) -6- (6-エタンスルホニ
5 ル-ピリジン-3-イルオキシ) -2-ピリジン-2-イル-1H-ベンズイ
ミダゾール

(工程 1)

4-ヒドロキシ-6- (6-エタンスルホニル-ピリジン-3-イルオキ
シ) -2-ピリジン-2-イル-1H-ベンズイミダゾールの合成

10 実施例 436 で得られた 4-ベンジルオキシ-6- (6-エタンスルホニ
ル-ピリジン-3-イルオキシ) -2-ピリジン-2-イル-1H-ベンズイ
ミダゾールを用いて、実施例 251 (工程 1) と同様の方法、これに準じた方
法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

(工程 2)

15 4- (2-シアノ-6-フルオロ-フェノキシ) -6- (6-エタンスルホ
ニル-ピリジン-3-イルオキシ) -2-ピリジン-2-イル-1H-ベンズ
イミダゾールの製造

4-ヒドロキシ-6- (6-エタンスルホニル-ピリジン-3-イルオキ
シ) -2-ピリジン-2-イル-1H-ベンズイミダゾール及び 2, 3-ジフ
20 ルオロベンゾニトリルを用いて、実施例 251 (工程 2) と同様の方法、これ
に準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得
た。

¹HNMR (CD₃OD) δ : 1.26 (3H, t, J=7.4 Hz), 3.4
0 (2H, q, J=7.4 Hz), 6.61 (1H, d, J=2.0 Hz),
25 7.28 (1H, d, J=2.0 Hz), 7.36-7.42 (1H, m),
7.48-7.54 (1H, m), 7.58-7.63 (2H, m), 7.6
5-7.69 (1H, m), 8.07 (2H, d, J=8.2 Hz), 8.3
8 (1H, d, J=7.8 Hz), 8.51 (1H, d, J=2.7 Hz),
8.82 (1H, d, J=4.7 Hz)

ESI-MS (m/e) : 516 [M+H]

実施例 439

4-(6-シアノピリジン-2-イルオキシ)-6-(4-エタンスルホン
5 ルーフエノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 438 (工程 1) で得られた 4-ヒドロキシ-6-(6-エタンスル
ホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベン
ズイミダゾール及び 2-クロロ-3-シアノピリジンを用いて、実施例 438
(工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ
10 ることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 1.26 (3H, t, $J=7.4\text{ Hz}$), 3.4
2 (2H, q, $J=7.4\text{ Hz}$), 7.21 (1H, d, $J=2.0\text{ Hz}$),
7.30 (1H, dd, $J=7.4, 5.1\text{ Hz}$), 7.48 (1H, d, J
=2.0 Hz), 7.58 (1H, dd, $J=5.1, 7.8\text{ Hz}$), 7.7
15 1 (1H, dd, $J=8.8, 2.9\text{ Hz}$), 8.00-8.05 (1H,
m), 8.11 (1H, d, $J=8.6\text{ Hz}$), 8.26-8.33 (3H,
m), 8.60 (1H, d, $J=2.7\text{ Hz}$), 8.78 (1H, d, $J=5.$
1 Hz)

ESI-MS (m/e) : 499 [M+H]

20

実施例 440

4-(2-シアノ-3-フルオロフェノキシ)-6-(6-エタンスルホニ
ル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイ
ミダゾール

25 2, 6-ジフルオロベンゾニトリルを用いて、実施例 439 と同様の方法、
これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
を得た。

^1H NMR (CD_3OD) δ : 1.26 (3H, t, $J=7.4\text{ Hz}$), 3.4
1 (2H, q, $J=7.4\text{ Hz}$), 6.91 (1H, d, $J=8.6\text{ Hz}$),

7.04 (1H, d, $J=1.8\text{ Hz}$), 7.13 (1H, t, $J=8.6\text{ Hz}$), 7.44 (1H, d, $J=1.8\text{ Hz}$), 7.55–7.64 (2H, m), 7.67 (1H, dd, $J=8.6, 3.2\text{ Hz}$), 8.00–8.06 (1H, m), 8.10 (1H, d, $J=8.6\text{ Hz}$), 8.33 (1H, d, $J=7.8\text{ Hz}$), 8.57 (1H, d, $J=2.3\text{ Hz}$), 8.78–8.81 (1H, m)

ESI-MS (m/e): 516 [M+H]

実施例 441

10 4-(2-カルバモイル-6-フルオロフェノキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

15 実施例 438 で得られた 4-(2-シアノ-6-フルオロフェノキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

20 $^1\text{H NMR}$ (CD_3OD) δ : 1.24 (3H, t, $J=7.4\text{ Hz}$), 3.40 (2H, q, $J=7.4\text{ Hz}$), 6.53 (1H, brs), 7.26 (1H, brs), 7.42–7.53 (2H, m), 7.57–7.62 (2H, m), 7.68 (1H, dd, $J=8.2, 3.9\text{ Hz}$), 8.07 (1H, d, $J=8.6\text{ Hz}$), 8.11–8.16 (1H, m), 8.41 (1H, d, $J=8.2\text{ Hz}$), 8.49 (1H, d, $J=2.7\text{ Hz}$), 8.88 (1H, d, $J=3.9\text{ Hz}$)

25 ESI-MS (m/e): 534 [M+H]

実施例 442

4-(2-シアノ-6-フルオロフェノキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイ

ミダゾール

実施例 4 3 7 で得られた 4-ベンジルオキシ-6-(6-エタンスルホニ
ル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイ
ミダゾールを用いて、実施例 4 3 8 と同様の方法、これに準じた方法又はこれ
5 らと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 3.4
0 (2H, q, $J=7.4\text{ Hz}$), 6.57 (1H, brs), 7.23 (1
H, brs), 7.46-7.51 (1H, m), 7.57-7.61 (1H,
m), 7.64-7.71 (2H, m), 8.06 (1H, d, $J=9.0\text{ Hz}$)
10 z), 8.51 (1H, d, $J=2.3\text{ Hz}$), 8.71 (1H, d, $J=2.3\text{ Hz}$), 8.78 (1H, s), 9.48 (1H, s)

ESI-MS (m/e): 517 $[\text{M}+\text{H}]$

実施例 4 4 3

15 4-(2-シアノ-5-フルオロフェノキシ)-6-(6-エタンスルホニ
ル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイ
ミダゾール

実施例 4 4 2 で得られた 4-ヒドロキシ-6-(6-エタンスルホニル-ピ
リジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダ
20 ザール及び 2, 4-ジフルオロベンゾニトリルを用いて、実施例 4 3 8 (工
程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
により、表題化合物を得た。

^1H NMR (CD_3OD) δ : 1.20 (3H, t, $J=7.4\text{ Hz}$), 3.4
1 (2H, q, $J=7.4\text{ Hz}$), 6.88 (1H, d, $J=10.2\text{ Hz}$),
25 6.98 (1H, d, $J=2.0\text{ Hz}$), 7.05-7.11 (1H, m),
7.39-7.44 (1H, m), 7.68 (1H, dd, $J=3.1, 8.0\text{ Hz}$),
7.89 (1H, dd, $J=8.8, 6.1\text{ Hz}$), 8.08-8.
12 (1H, m), 8.57-8.60 (1H, m), 8.71 (1H, d,
 $J=2.3\text{ Hz}$), 8.77-8.79 (1H, m), 9.46-9.48

(1H, m)

ESI-MS (m/e) : 517 [M+H]

実施例 444

5 4-(2-シアノ-4-フルオロフェノキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

2, 5-ジフルオロベンゾニトリルを用いて、実施例 443 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
10 を得た。

^1H NMR (CD_3OD) δ : 1.26 (3H, t, $J=7.4\text{ Hz}$), 3.41 (2H, q, $J=7.4\text{ Hz}$), 6.81 (1H, d, $J=2.3\text{ Hz}$), 7.22 (1H, dd, $J=4.6, 9.0\text{ Hz}$), 7.35 (1H, d, $J=2.3\text{ Hz}$), 7.45 (1H, ddd, $J=8.6, 4.6, 7.4\text{ Hz}$),
15 7.63-7.69 (2H, m), 7.72-7.75 (1H, m), 8.09 (1H, d, $J=8.6\text{ Hz}$), 8.55 (1H, d, $J=3.1\text{ Hz}$), 8.72 (1H, d, $J=2.3\text{ Hz}$), 8.79 (1H, dd, $J=2.0, 3.1\text{ Hz}$), 9.49 (1H, d, $J=2.0\text{ Hz}$)

ESI-MS (m/e) : 517 [M+H]

20

実施例 445

4-(2-カルバモイル-6-フルオロフェノキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

25 実施例 442 で得られた 4-(2-シアノ-6-フルオロフェノキシ)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾールを用いて、実施例 43 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 3.39 (2H, q, $J=7.4\text{ Hz}$), 6.39 (1H, s), 7.21 (1H, s), 7.42–7.51 (2H, m), 7.55 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 7.64 (1H, d, $J=7.4\text{ Hz}$), 8.06 (1H, d, $J=8.6\text{ Hz}$), 8.47 (1H, d, $J=2.7\text{ Hz}$), 8.75–8.78 (1H, m), 8.82–8.84 (1H, m), 9.54 (1H, br s)

ESI-MS (m/e): 535 [$\text{M}+\text{H}$]

10 実施例 446

4-(6-シアノピリジン-2-イルオキシ)-6-(4-エタンスルホンルフェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

2-クロロ-3-シアノピリジンを用いて、実施例 443 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を

15 得た。

^1H NMR (CD_3OD) δ : 1.25 (3H, t, $J=7.4\text{ Hz}$), 3.41 (2H, q, $J=7.4\text{ Hz}$), 7.14 (1H, d, $J=2.0\text{ Hz}$), 7.30 (1H, dd, $J=7.4, 5.1\text{ Hz}$), 7.45 (1H, d, $J=2.0\text{ Hz}$), 7.69 (1H, dd, $J=9.0, 2.7\text{ Hz}$), 8.10 (1H, d, $J=9.0\text{ Hz}$), 8.27–8.33 (2H, m), 8.59 (1H, d, $J=2.7\text{ Hz}$), 8.70–8.72 (1H, m), 8.76–8.79 (1H, m), 9.41–9.43 (1H, m)

ESI-MS (m/e): 500 [$\text{M}+\text{H}$]

25 実施例 447

4-(2-シアノ-6-フルオロフェノキシ)-6-(6-メタンスルホンルピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

6-メタンスルホンルピリジン-3-オールを用いて、実施例 438 と同

様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CD_3OD) δ : 3.23 (3H, s), 6.50 (1H, s),
 7.22 (1H, s), 7.45–7.62 (3H, m), 7.62–7.7
 5 8 (2H, m), 7.95–8.05 (1H, m), 8.08 (1H, d, J
 = 8.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.49 (1H,
 s), 8.77 (1H, s)
 ESI-MS (m/e): 502 [M+H]

10 実施例 448

4-(2-フルオロ-6-メタンスルホニルフェノキシ)-6-(6-メタ
ンスルホニルピリジン-3-イルオキシ)-2-ピリジン-2-イル-1
H-ベンズイミダゾール

実施例 447 で得られた 4-ヒドロキシ-6-(6-メタンスルホニルピ
 15 リジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダ
 ザール及び 2,3-ジフルオロ-メタンスルホニルベンゼンを用いて、実施例
 438 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み
 合わせるにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 3.21 (3H, s), 3.46 (3H, s),
 20 6.54 (1H, d, J = 2.0 Hz), 7.27 (1H, d, J = 2.0 Hz),
 7.54–7.67 (3H, m), 7.70–7.74 (1H, m),
 7.93 (1H, d, J = 7.8 Hz), 8.04 (1H, d, J = 8.6 Hz),
 8.11 (1H, ddd, J = 7.8, 8.6, 2.7 Hz), 8.4
 0 (1H, d, J = 7.8 Hz), 8.46 (1H, d, J = 2.7 Hz),
 25 8.86 (1H, d, J = 5.1 Hz)
 ESI-MS (m/e): 555 [M+H]

実施例 449

4-(2-カルバモイル-6-フルオロフェノキシ)-6-(6-メタンス

ルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例447で得られた4-(2-シアノ-6-フルオロ-フェノキシ)-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾールを用いて、実施例43と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.22 (3H, s), 6.53 (1H, d, $J=1.6\text{ Hz}$), 7.25 (1H, d, $J=1.6\text{ Hz}$), 7.42-7.53 (2H, m), 7.57 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 7.61 (1H, d, $J=7.4\text{ Hz}$), 7.68 (1H, dd, $J=7.6, 4.3\text{ Hz}$), 8.06 (1H, d, $J=9.0\text{ Hz}$), 8.10-8.16 (1H, m), 8.41 (1H, d, $J=8.2\text{ Hz}$), 8.47 (1H, d, $J=2.7\text{ Hz}$), 8.87 (1H, d, $J=4.3\text{ Hz}$)

ESI-MS (m/e): 520 $[\text{M}+\text{H}]$

実施例450

4-(2-シアノ-6-フルオロ-フェノキシ)-6-(6-メタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

6-メタンスルホニル-ピリジン-3-オールを用いて、実施例442と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

$^1\text{H NMR}$ (CD_3OD) δ : 3.23 (3H, s), 6.57 (1H, br s), 7.23 (1H, br s), 7.49 (1H, td, $J=8.0, 4.6\text{ Hz}$), 7.59 (1H, dd, $J=9.0, 3.2\text{ Hz}$), 7.65-7.71 (2H, m), 8.07 (1H, d, $J=9.0\text{ Hz}$), 8.50 (1H, d, $J=2.3\text{ Hz}$), 8.71 (1H, d, $J=2.3\text{ Hz}$), 8.78 (1H, br s), 9.48 (1H, br s)

ESI-MS (m/e) : 503 [M+H]

実施例 451

4- (ピリジン-2-イルスルファニル) -6- (6-エタンスルホニル-ピ
5 リジン-3-イルオキシ) -2-ピリジン-2-イル-1H-ベンズイミダ
ゾール

6-エタンスルホニル-ピリジン-3-オールを用いて、実施例 288 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡褐色固体として得た。

10 ^1H NMR (CDCl_3) δ : 1.31 (3H, t, $J=7.4\text{ Hz}$), 3.39 (2H, q, $J=7.4\text{ Hz}$), 7.03 (1H, d, $J=8.0\text{ Hz}$), 7.08 (1H, ddd, $J=7.4, 4.7, 1.0\text{ Hz}$), 7.35 (1H, d, $J=2.2\text{ Hz}$), 7.38-7.44 (2H, m), 7.52 (1H, td, $J=7.8, 2.0\text{ Hz}$), 7.64 (1H, d, $J=2.1\text{ Hz}$),
15 z), 7.88 (1H, td, $J=7.8, 1.8\text{ Hz}$), 8.03 (1H, d, $J=8.8\text{ Hz}$), 8.38 (1H, d, $J=7.8\text{ Hz}$), 8.45 (1H, dd, $J=4.9, 1.0\text{ Hz}$), 8.53 (1H, d, $J=2.7\text{ Hz}$), 8.64 (1H, d, $J=4.9\text{ Hz}$)

ESI-MS (m/e) : 490 [M+H]

20

実施例 452

4- (ピリジン-2-イルスルファニル) -6- (6-エタンスルホニル-ピ
リジン-3-イルオキシ) -2-ピラジン-2-イル-1H-ベンズイミダ
ゾール

25 実施例 451 で得られた 3- (ピリジン-2-イルスルファニル) -5- (6-エタンスルホニル-ピリジン-3-イルオキシ) -ベンゼン-1, 2-ジアミンを用いて、実施例 68 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.32 (3H, t, $J=7.4\text{ Hz}$), 3.3

9 (2H, q, $J=7.4$ Hz), 7.08–7.19 (2H, m), 7.3
 8 (1H, d, $J=2.2$ Hz), 7.43 (1H, dd, $J=8.6, 2.$
 8 Hz), 7.57 (1H, td, $J=7.8, 1.8$ Hz), 7.66 (1
 H, d, $J=2.2$ Hz), 8.04 (1H, d, $J=8.6$ Hz), 8.4
 5 8 (1H, d, $J=4.7$ Hz), 8.53 (1H, d, $J=2.7$ Hz),
 8.63 (1H, t, $J=2.0$ Hz), 8.69 (1H, d, $J=2.5$ H
 z), 9.63 (1H, d, $J=1.4$ Hz)
 ESI-MS (m/e): 491 [M+H]

10 実施例 453

4-(1-メチル-1H-イミダゾール-2-イルスルファニル)-6-
(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-
イル-1H-ベンズイミダゾール

1-メチル-1H-イミダゾール-2-チオールを用いて、実施例 452 と
 15 同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
 表題化合物を黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.33 (3H, t, $J=7.4$ Hz), 3.4
 1 (2H, q, $J=7.4$ Hz), 3.94 (3H, s), 6.65–6.6
 9 (1H, m), 6.77 (1H, d, $J=1.4$ Hz), 6.87 (1H,
 20 d, $J=1.6$ Hz), 7.23 (1H, d, $J=2.4$ Hz), 7.48
 (1H, dd, $J=8.6, 2.8$ Hz), 7.72 (1H, d, $J=2.2$
 Hz), 8.05 (1H, dd, $J=8.6, 0.6$ Hz), 8.16 (1H,
 d, $J=2.6$ Hz), 8.54 (1H, dd, $J=2.8, 0.6$ Hz),
 9.42 (1H, d, $J=1.6$ Hz)

25 ESI-MS (m/e): 494 [M+H]

実施例 454

4-(4-メトキシベンジル-スルファニル)-6-(6-エタンスルホニ
ル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイ

ミダゾール

(4-メトキシフェニル)メタンチオールを用いて、実施例452と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を褐色固体として得た。

- 5 $^1\text{H NMR}$ (CDCl_3) δ : 1.32 (3H, t, $J=7.4\text{ Hz}$), 3.40 (2H, q, $J=7.4\text{ Hz}$), 3.61 and 3.79 (total 3H, each s), 4.05 and 4.40 (total 2H, each s), 6.69 and 6.79 (total 2H, each d, $J=8.6\text{ Hz}$), 6.88–7.52 (5H, m), 7.98 and
- 10 8.01 (total 1H, each d, $J=8.6\text{ Hz}$), 8.44 and 8.46 (total 1H, each d, $J=2.9\text{ Hz}$), 8.58–8.65 (1H, m), 8.68 and 8.70 (total 1H, each d, $J=2.5\text{ Hz}$), 9.58 and 9.74 (total 1H, each d, $J=1.4\text{ Hz}$), 10.05 and 10.
- 15 46 (total 1H, each brs)
ESI-MS (m/e): 534 $[\text{M}+\text{H}]$

実施例455

- 4-(6-シアノピリジン-2-イルスルファニル)-6-(6-エタンス
- 20 ルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

2-クロロ-3-シアノピリジンを用いて、実施例446と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- 25 $^1\text{H NMR}$ (CDCl_3) δ : 1.32 (3H, t, $J=7.4\text{ Hz}$), 3.39 (2H, q, $J=7.4\text{ Hz}$), 7.20 (1H, dd, $J=7.8, 4.9\text{ Hz}$), 7.41 (1H, d, $J=2.2\text{ Hz}$), 7.45 (1H, dd, $J=8.8, 2.8\text{ Hz}$), 7.72 (1H, d, $J=2.2\text{ Hz}$), 7.93 (1H, dd, $J=7.8, 1.8\text{ Hz}$), 8.04 (1H, d, $J=8.$

6 Hz), 8.44 (1H, dd, $J=4.9, 2.0$ Hz), 8.54 (1H, d, $J=2.8$ Hz), 8.62 (1H, dd, $J=2.5, 1.5$ Hz), 8.70 (1H, d, $J=2.5$ Hz), 9.64 (1H, d, $J=1.5$ Hz)

5 ESI-MS (m/e): 516 [M+H]

実施例 456

4-(2-シアノ-ピリジン-3-イルスルファニル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

10

実施例 455 で得られた 4-メルカプト-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール及び 2-シアノ-3-フルオロピリジンを用いて、実施例 438 (工程 2) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

15

^1H NMR (DMSO- d_6) δ : 1.13 (3H, t, $J=7.4$ Hz), 3.40 (2H, q, $J=7.4$ Hz), 7.22 (1H, s), 7.41 (1H, s), 7.64 (2H, dd, $J=8.6, 2.7$ Hz), 7.96-8.04 (2H, m), 8.59-8.66 (2H, m), 8.77-8.83 (2H, m), 9.32 (1H, s)

20

ESI-MS (m/e): 516 [M+H]

実施例 457

4-(ピリジン-2-イルスルファニル)-5-クロロ-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

25

ピリジン-2-チオールを用いて、実施例 117 及び実施例 290 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.31 (3H, t, $J=7.4\text{ Hz}$), 3.40 (2H, q, $J=7.4\text{ Hz}$), 7.02 (1H, d, $J=7.5\text{ Hz}$), 7.05–7.10 (1H, m), 7.31 (1H, dd, $J=8.6, 2.7\text{ Hz}$), 7.41 (1H, t, $J=6.0\text{ Hz}$), 7.53 (1H, t, $J=7.4\text{ Hz}$), 7.75 (1H, s), 7.88 (1H, t, $J=7.8\text{ Hz}$), 8.03 (1H, d, $J=8.8\text{ Hz}$), 8.37 (1H, d, $J=8.0\text{ Hz}$), 8.41 (1H, d, $J=4.1\text{ Hz}$), 8.50 (1H, d, $J=2.5\text{ Hz}$), 8.63 (1H, s)
ESI-MS (m/e): 524, 526 $[\text{M}+\text{H}]$

10

実施例458-1、458-2

4-(ピリジン-2-イルスルフィニル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール、及び4-(ピリジン-2-イルスルホニル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例451で得られた4-(ピリジン-2-イルスルファニル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール20mgのメタノール3ml溶液に、OXONE 50mg、及び水0.5mlを加え、反応液を室温にて3時間攪拌した。溶媒を減圧留去し、得られた残渣を酢酸エチルで希釈し、水で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣を逆相中圧液体クロマトグラフィー[ODS-AS-360-CC(YMC社製)移動相: 水-アセトニトリル-0.1%トリフルオロ酢酸]にて精製した。得られたフラクションに飽和炭酸水素ナトリウム水を加えた後、酢酸エチルにて抽出し、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、表題化合物を得た。

25

4-(ピリジン-2-イルスルフィニル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダ

ゾール

- ¹HNMR (CDCl₃) δ : 1.33 (3H, t, J=7.4 Hz), 3.40 (2H, q, J=7.4 Hz), 7.35 (1H, dd, J=8.8, 2.7 Hz), 7.37-7.45 (2H, m), 7.55 (1H, d, J=2.1 Hz), 7.61 (1H, d, J=2.1 Hz), 7.89 (1H, t, J=7.8 Hz), 7.96 (1H, t, J=7.8 Hz), 8.02 (1H, d, J=8.6 Hz), 8.15 (1H, d, J=8.2 Hz), 8.37 (1H, d, J=7.8 Hz), 8.49 (1H, d, J=2.7 Hz), 8.65 (1H, d, J=3.7 Hz), 8.76 (1H, d, J=4.5 Hz)
- ESI-MS (m/e) : 506 [M+H]

4-(ピリジン-2-イルスルホニル)-6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- ¹HNMR (CDCl₃) δ : 1.33 (3H, t, J=7.4 Hz), 3.40 (2H, q, J=7.4 Hz), 7.37 (1H, dd, J=8.6, 2.8 Hz), 7.44-7.49 (1H, m), 7.55 (1H, dd, J=7.4, 4.5 Hz), 7.70 (1H, d, J=1.8 Hz), 7.80 (1H, d, J=2.2 Hz), 7.88-7.94 (1H, m), 7.96-8.02 (1H, m), 8.04 (1H, d, J=8.6 Hz), 8.26 (1H, d, J=7.4 Hz), 8.40 (1H, d, J=8.0 Hz), 8.49 (1H, d, J=2.7 Hz), 8.73 (1H, d, J=4.7 Hz), 8.77 (1H, d, J=4.9 Hz)
- ESI-MS (m/e) : 522 [M+H]

25 実施例 459

6-(1-アセチルピロリジン-2-イル)-5-(2'-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

2'-フルオロビフェニル-4-オールを用いて、実施例 338 (工程 5)

と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.00–2.60 (7H, m), 3.40–4.00 (2H, m), 5.20–5.65 (1H, m), 7.00–7.70

5 (11H, m), 7.80–8.00 (1H, m), 8.25–8.45 (1H, m), 8.50–8.70 (1H, m)

ESI-MS (m/e): 493 $[\text{M}+\text{H}]$

実施例460

10 6 – (1 – アセチルピロリジン – 2 – イル) – 5 – (4 – (ジフルオロメチル) フェノキシ) – 2 – ピリジン – 2 – イル – 1H – ベンズイミダゾール – トリフルオロ酢酸塩

(工程1)

15 4 – (6 – (1 – (アセチルピロリジン – 2 – イル) – 2 – ピリジン – 2 – イル – 1 – ((2 – (トリメチルシリル) エトキシ) メチル) – 1H – ベンズイミダゾール – 5 – イル) オキシ) ベンズアルデヒドの合成

実施例121 (工程11) で得られた、1 – (2 – (6 – ヒドロキシ – 2 – ピリジン – 2 – イル – 3 – (2 – トリメチルシリル – エトキシメチル) – 3H – ベンズイミダゾール – 5 – イル) – ピロリジン – 1 – イル) – エタノン1
20 00mg のN – メチル – 2 – ピロリジドン1ml 溶液に、炭酸セシウム143mg、p – フルオロベンズアルデヒド0.048ml を順次加え、反応液を80度にて3時間加熱攪拌した。反応液を室温に冷却後、飽和塩化アンモニウム水溶液を加え、酢酸エチルで抽出し、有機層を飽和食塩水で洗浄した。乾燥後、溶媒を減圧留去し、残渣をシリカゲルカラムクロマトグラフィー (展開溶媒:
25 クロロホルム/メタノール=100/1) で精製し、表題化合物を橙色油状物質として得た。

(工程2)

6 – (1 – アセチルピロリジン – 2 – イル) – 5 – (4 – (ジフルオロメチル) フェノキシ) – 2 – ピリジン – 2 – イル – 1H – ベンズイミダゾールの合

成

4 - (6 - (1 - (アセチルピロリジン-2-イル) - 2-ピリジン-2-イル-1 - ((2 - (トリメチルシリル) エトキシ) メチル) - 1H-ベンズイミダゾール-5-イル) オキシ) ベンズアルデヒド 22 mg のクロロホルム
 5 0.2 ml 溶液に、ビス(2-メトキシエチル) アミノサルファートリフロライド 0.036 ml を加え、反応液を 80 度にて 8 時間加熱攪拌した。溶媒を減圧留去した後、分取用薄層クロマトグラフィー (Kieselgel TM 60 F 254、Art 5744 (メルク社製)、ヘキサン/酢酸エチル = 1/1) で精製し、表題化合物を黄色固体として得た。

10 (工程 3)

6 - (1-アセチルピロリジン-2-イル) - 5 - (4 - (ジフルオロメチル) フェノキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール-トリフルオロ酢酸塩の製造

6 - (1-アセチルピロリジン-2-イル) - 5 - (4 - (ジフルオロメチル) フェノキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール 12
 15 mg にトリフルオロ酢酸 0.5 ml を加え、反応液を室温で 1 時間攪拌した。トリフルオロ酢酸を減圧留去した後、残渣を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションの溶媒を減圧
 20 留去し、表題化合物を赤色油状物として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 0.78-0.95 (4H, m), 1.91-2.15 (2H, m), 2.69 (3H, s), 5.38-5.43 (1H, m), 7.21-7.34 (4H, m), 7.52-7.63 (6H, m), 8.27-8.29 (1H, m)

25 ESI-MS (m/e): 449 [M+H]

実施例 461

1 - (2 - (6 - (3-クロロ-4-メタンスルホニル-フェノキシ) - 2-ピリジン-2-イル-3H-ベンゾイミダゾール-5-イル) - ピロリジン-

1-イル)-エタノン

(3-クロロ-4-メタンシルホニル)フェノールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 5 $^1\text{H NMR}$ (CDCl_3) δ : 1.85–2.40 (4H, m), 2.90–3.27 (5H, m), 3.65–3.90 (2H, m), 5.15–5.43 (1H, m), 6.90–7.45 (5H, m), 7.84–8.15 (2H, m), 8.35–8.42 (1H, m), 8.60–8.68 (1H, m)
ESI-MS (m/e): 511 [M+H]

10

実施例462

2-(6-(1-アセチルピロリジン-2-イル)-5-(4-(メタンシルホニル)フェノキシ)-1H-ベンズイミダゾール-2-イル)(1,3)チアゾロ(5,4-b)ピリジン・トリフルオロ酢酸塩

- 15 実施例306(工程3)で得られた2-(4,5-ジアミノ-2-(4-メタンシルホニルフェノキシ)-フェニル)-ピロリジン-1-カルボン酸t-ブチルエステル、及び(1,3)チアゾロ(5,4-b)ピリジン-2-カルボン酸を用いて、実施例306(工程4)及び(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
20 を黄色油状物質として得た。

- $^1\text{H NMR}$ (CD_3OD) δ : 1.60–2.40 (7H, m), 3.00–3.80 (5H, m), 5.00–5.60 (1H, m), 7.20–7.40 (2H, m), 7.25–7.80 (3H, m), 7.90–8.10 (2H, m), 8.40–8.80 (2H, m)
25 ESI-MS (m/e): 534 [M+H]

実施例463

5-(1-アセチルピロリジン-2-イル)-6-(4-(メタンシルホニル)フェノキシ)-2-(5-(トリフルオロメチル)ピリジン-2-イ

ル) -1H-ベンズイミダゾール

5 - (トリフルオロメチル) ピリジン-2-カルボン酸を用いて、実施例 4 6 2 と同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 0.89 (1H, m), 1.22 (2H, m),
1.88-2.11 (3H, m), 2.27 (1H, m), 3.08 (3H,
m), 3.63-3.76 (1H, m), 3.84 (1H, s), 5.38
(1H, dd, $J=25.8, 8.6\text{ Hz}$), 7.11-7.20 (2H,
m), 7.39 (1H, m), 7.54 (1H, m), 7.93 (2H, m),
10 8.11 (1H, m), 8.51 (1H, m), 8.93 (1H, m), 10.
58-10.88 (1H, m)
ESI-MS (m/e): 545 $[\text{M}+\text{H}]$

実施例 4 6 4

- 15 6 - (1-アセチルピロリジン-2-イル) - 2 - (5 - (ジフルオロメチル) ピリジン-2-イル) - 5 - (4-メタンスルホニル) フェノキシ) - 1
H-ベンズイミダゾール・トリフルオロ酢酸塩

- 5 - (ジフルオロメチル) ピリジン-2-カルボン酸を用いて、実施例 4 6 2 と同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

- 20 $^1\text{H-NMR}$ (CD_3OD) δ : 0.92 (1H, m), 1.32 (2H, m),
1.89 (1H, m), 1.97-2.08 (2H, m), 2.13-2.14 (1H, m), 2.69 (3H, s), 3.16-3.17 (3H, s),
5.35 (1H, m), 7.30-7.32 (1H, m), 7.41-7.5
25 8 (1H, m), 7.60-7.62 (1H, m), 8.00-8.02 (3
H, m), 8.04-8.22 (2H, m), 9.04 (1H, m)
ESI-MS (m/e): 527 $[\text{M}+\text{H}]$

実施例 4 6 5

6-(1-アセチルピロリジン-2-イル)-5-(4-(メトキシメチル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール・トリフルオロ酢酸塩

- 実施例 460 (工程 1) で得られた、4-(6-(1-(アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1-((2-(トリメチルシリル)エトキシ)メチル)-1H-ベンズイミダゾール-5-イル)オキシ)ベンズアルデヒド 50 mg のメタノール 0.5 ml 溶液に、氷冷下、水酸化ホウ素ナトリウム 7 mg を加え、反応液を 1 時間攪拌した。反応液に飽和塩化アンモニウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧留去し、粗生成物を得た。得られた粗生成物のジメチルホルムアミド 1 ml 溶液に、水素化ナトリウム 10 mg、及びヨウ化メチル 0.030 ml を順次加え、室温で 30 分間攪拌した。反応液に飽和塩化アンモニウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧留去し粗生成物を得た。得られた粗生成物にトリフルオロ酢酸 0.5 ml を加え、反応液を室温にて 2 時間攪拌した。トリフルオロ酢酸を減圧留去した後、残渣を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションの溶媒を減圧留去し、表題化合物を黄色油状物として得た。
- $^1\text{H NMR}$ (CD_3OD) δ : 1.93 (1H, m), 2.07-2.11 (3H, m), 2.18 (2H, m), 2.45 (1H, m), 3.43 (3H, d, $J=3.1\text{ Hz}$), 3.75-3.95 (2H, m), 4.50 (d, 2H, $J=4.3\text{ Hz}$), 5.49-5.56 (1H, m), 7.16 (3H, m), 7.44-7.49 (2H, m), 7.57 (1H, m), 7.70-7.73 (1H, m), 8.15 (1H, m), 8.27-8.30 (1H, m), 8.89 (1H, m)
- ESI-MS (m/e): 443 [$M+H$]

1 - (4 - (6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) エタノール・トリフルオロ酢酸塩

実施例 460 (工程 1) で得られた、4 - (6 - (1 - (アセチルピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 - ((2 - (トリメチルシリル) エトキシ) メチル) - 1 H - ベンズイミダゾール - 5 - イル) オキシ) ベンズアルデヒド 70 mg のテトラヒドロフラン 1.3 ml 溶液に、-78 度にてメチルリチウム (1.0 M ジエチルエーテル溶液) 0.4 ml を加え、反応液を -78 度にて 30 分間攪拌した。反応液に飽和塩化アンモニウム溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧留去し、粗生成物を得た。得られた粗生成物にトリフルオロ酢酸 0.5 ml を加え、室温で 90 分間攪拌した後、トリフルオロ酢酸を減圧留去し、残渣を逆相中圧液体クロマトグラフィー [ODS-AS-360-CC (YMC 社製) 移動相: 水-アセトニトリル-0.1% トリフルオロ酢酸] にて精製し、得られたフラクションの溶媒を減圧留去し、表題化合物を黄色油状物として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 0.90-0.96 (1H, m), 1.31 (4H, m), 1.25-1.90 (3H, m), 2.42 (1H, m), 2.68 (3H, s), 3.89-3.91 (1H, m), 5.50 (1H, m), 7.02-7.33 (4H, m), 7.42-7.52 (2H, m), 7.59-7.67 (1H, m), 8.10-8.14 (1H, m), 8.22-8.26 (1H, m), 8.80-8.87 (1H, m)

ESI-MS (m/e): 443 [$M+H$]

25 実施例 467

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (3 - メチル - [1, 2, 4] - オキサジアゾール - 5 - イル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール

5 - (4 - ヨウドフェニル) - 3 - メチル - [1, 2, 4] - オキサジア

ゾールを用いて、実施例 122 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を茶褐色油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.39–2.49 (10H, m), 3.42–3.88 (2H, m), 5.14–5.4 (1H, m), 6.70–8.69 (10H, m)

ESI-MS (m/e): 481 $[\text{M}+\text{H}]$

実施例 468

10 (1-アセチル-2-(5-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1 H-ベンズイミダゾール-6-イル)ピロリジン-3-イルアセテート ジアステレオマーA

(工程 1)

3-(t -ブチル(ジメチル)シリル)オキシ)ジヒドロフラン-2(3H)-オンの合成

15 3-ヒドロキシジヒドロフラン-2(3H)-オン 9.0 g のジメチルホルムアミド 180 ml 溶液に、イミダゾール 9.0 g、 t -ブチルジメチルシリルクロリド 15.9 g を順次加え、反応液を室温にて 1 時間攪拌した。反応液を酢酸エチルにて希釈し、水にて洗浄した後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=5/1)により精製し、表題化合物を無色油状物質として得た。

(工程 2)

N-(4-(2-(t -ブチル(ジメチル)シリル)オキシ)-4-ヒドロキシブタノイル)-3-フルオロフェニル)ピリジン-2-カルボキサミドの合成

25 N-(4-ブロモ-3-フルオロフェニル)ピリジン-2-カルボキサミド 1.1 g のテトラヒドロフラン 100 ml 溶液に、 -78°C にて、 n -ブチルリチウム (2.66 M ヘキサン溶液) 3.1 ml を滴下し、反応液を同温にて 15 分間攪拌した。反応液に 3-(t -ブチル(ジメチル)シリル)オキシ)ジヒドロフラン-2(3H)-オン 1.21 g を加え、反応液を同温にて 1 時

間攪拌した。同温にて反応液に飽和重曹水を加え、室温に昇温した後、酢酸エチルにて抽出した。有機層を無水硫酸ナトリウムで乾燥後、溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝１００／１）により精製し、表題化合物を無色油状物質として得た。

5 (工程３)

N-（４-（２-（（ｔ-ブチル（ジメチル）シリル）オキシ）-１，４-ジヒドロキシブチル）-３-フルオロフェニル）ピリジン-２-カルボキサミドの合成

10 N-（４-（２-（（ｔ-ブチル（ジメチル）シリル）オキシ）-４-ヒドロキシブタノイル）-３-フルオロフェニル）ピリジン-２-カルボキサミド 860 mg のメタノール 20 ml 溶液に、氷冷下、水素化ホウ素ナトリウム 114 mg を加え、反応液を室温にて 30 分間攪拌した。反応液に飽和重曹水を加え、クロロホルムにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー（展開溶媒：クロロホルム／メ
15 タノール＝１００／１）により精製し、表題化合物を白色固体として得た。

(工程４)

N-（４-（３-（（ｔ-ブチル（ジメチル）シリル）オキシ）ピロリジン-２-イル）-３-フルオロフェニル）ピリジン-２-カルボキサミドの合成

20 N-（４-（２-（（ｔ-ブチル（ジメチル）シリル）オキシ）-１，４-ジヒドロキシブチル）-３-フルオロフェニル）ピリジン-２-カルボキサミド 165 mg のクロロホルム 8 ml 溶液に、氷冷下、トリエチルアミン 155 mg、メタンスルホニルクロリド 130 mg を順次加え、反応液を室温にて 30 分間攪拌した。反応液をクロロホルムにて希釈し、飽和重曹水にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のジメチルホルム
25 アミド 5 ml 溶液に、アジ化ナトリウム 25 mg を加え、反応液を 40 度にて 2 時間攪拌した。反応液を冷却後、水を加え、酢酸エチルにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のメタノール 10 ml 溶液に、水素化ホウ素ナトリウム 50 mg、硫酸銅・五水和物 5 mg を順次加え、反応液を 40 度にて 2 時間攪拌した。反応液を冷却後、飽和重曹水を

加え、クロロホルムにて抽出した後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝50／1）により精製し、表題化合物を無色油状物質として得た。

5 (工程5)

1-アセチル-2-(2-フルオロ-4-(（ピリジン-2-イルカルボニル）アミノ)フェニル)ピロリジン-3-イルアセテート

の合成

- 10 N-(4-(3-(（t-ブチル（ジメチル）シリル）オキシ）ピロリジン-2-イル)-3-フルオロフェニル)ピリジン-2-カルボキサミド59mgのメタノール1ml溶液に、4規定塩酸-ジオキサン2mlを加え、反応液を室温にて1時間攪拌した。溶媒を減圧留去し、得られた残渣のクロロホルム5ml溶液にトリエチルアミン100mg、無水酢酸90mg、N,N-4-ジメチルアミノピリジン5mgを順次加え、反応液を室温にて15分間攪拌した。溶媒
- 15 を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー（展開溶媒：クロロホルム／メタノール＝200／1）により精製し、表題化合物を無色油状物質として得た

(工程6)

- 20 1-アセチル-2-(2-フルオロ-5-ニトロ-4-(（ピリジン-2-イルカルボニル）アミノ)フェニル)ピロリジン-3-イルアセテート ジアステレオマーA及びジアステレオマーBの合成

- 25 N-(4-(3-(（t-ブチル（ジメチル）シリル）オキシ）ピロリジン-2-イル)-3-フルオロフェニル)ピリジン-2-カルボキサミド57mgに発煙硝酸1mlを加え、反応液を室温にて40分間攪拌した。反応液を氷-飽和重曹水混合溶液中に注ぎ、クロロホルムにて抽出した後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し得られた残渣を、分取用薄層クロマトグラフィー（KieselgelTM60F₂₅₄、Art 5744（メルク社製）、クロロホルム／メタノール＝20／1）にて精製し、表題化合物のジアステレオマーA、及びジアステレオマーBをそれぞれ黄色油状物質として得た。

(工程 7)

1-アセチル-2-(5-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1 H-ベンズイミダゾール-6-イル)ピロリジン-3-イルアセテート ジアステレオマーA の製造

- 5 4-(メタンスルホニル)フェノール、及び(1-アセチル-2-(2-フルオロ-5-ニトロ-4-(ピリジン-2-イルカルボニル)アミノ)フェニル)ピロリジン-3-イルアセテート ジアステレオマーA を用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。
- 10 $^1\text{H NMR}$ (CDCl_3) δ : 1.86-2.42 (8H, m), 3.04-3.10 (3H, m), 3.72-4.02 (2H, m), 5.06-5.38 (2H, m), 7.08-7.70 (5H, m), 7.83-7.97 (3H, m), 8.34-8.42 (1H, m), 8.61-8.68 (1H, m), 10.54-10.65 (1H, m)
- 15 ESI-MS (m/e): 535 [$\text{M}+\text{H}$]

実施例 469

1-アセチル-2-(5-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1 H-ベンズイミダゾール-6-イル)ピロリジン-3-オール

20 ジアステレオマーA

- 実施例 468 で得られた (1-アセチル-2-(5-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1 H-ベンズイミダゾール-6-イル)ピロリジン-3-イルアセテート ジアステレオマーA 14mg のメタノール 2ml 溶液に、炭酸カリウム 5mg を加え、反応液を室温にて一終夜攪拌した。溶媒を減圧留去し、得られた残渣を得られた残渣を分取用薄層クロマトグラフィー ($\text{Kieselgel}^{\text{TM}} 60 \text{ F}_{254}$, Art 5744 (メルク社製)、クロロホルム/メタノール=15/1) により精製し、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.82-2.47 (5H, m), 3.05 & 3.

0.8 (3H, s), 3.70–3.97 (2H, m), 4.29–4.45
 (1H, m), 5.00–5.32 (1H, m), 7.00–7.67 (5H,
 m), 7.81–7.96 (2H, m), 8.00–8.42 (1H, m),
 8.60–8.69 (1H, m), 10.62–10.85 (1H, m)

5 ESI-MS (m/e) : 493 [M+H]

実施例 470

6 – (1-アセチル-4, 5-ジヒドロ-1 H-ピロール-2-イル) – 5 –
(4 – (メタンスルホニル) フェノキシ) – 2 – ピリジン – 2 – イル – 1 H – ベ
 10 ンズイミダゾール

実施例 469 で得られた、1-アセチル-2-(5 – (4 – (メタンスルホニ
 ル) フェノキシ) – 2 – ピリジン – 2 – イル – 1 H – ベンズイミダゾール – 6 –
 イル)ピロリジン – 3 – オール ジアステレオマー A 2 mg のクロロホルム 1 ml
 15 g を加え、反応液を室温にて 15 分間攪拌した。溶媒を減圧留去し、得られた
 残渣を分取用薄層クロマトグラフィー (Kieselgel™ 60 F₂₅₄, Ar
 t 5744 (メルク社製)、クロロホルム/メタノール = 15/1) により精
 製し、表題化合物を無色油状物質として得た。

¹H NMR (CDCl₃) δ : 1.40–4.43 (10H, m), 7.03–
 20 7.80 (6H, m), 7.82–7.95 (3H, m), 8.32–8.4
 6 (1H, m), 8.60–8.71 (1H, m), 10.38–10.60
 (1H, m)

ESI-MS (m/e) : 475 [M+H]

25 実施例 471

1-アセチル-2-(5 – (4 – (メタンスルホニル) フェノキシ) – 2 – ピリジ
ン – 2 – イル – 1 H – ベンズイミダゾール – 6 – イル)ピロリジン – 3 – イルア
セテート ジアステレオマー B

実施例 468 (工程 6) で得られた、(1-アセチル-2-(2-フルオロ-

5-ニトロ-4-((ピリジン-2-イルカルボニル)アミノ)フェニル)ピロリジン-3-イル) ジアステレオマーBを用いて、実施例468(工程7)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- 5 $^1\text{H NMR}$ (CDCl_3) δ : 1.72–2.30 (8H, m), 3.02–3.08 (3H, m), 3.64–3.99 (2H, m), 5.26–5.47 (1H, m), 5.58–5.72 (1H, m), 7.09–7.73 (5H, m), 7.82–7.94 (3H, m), 8.33–8.43 (1H, m), 8.60–8.70 (1H, m), 10.47–10.68 (1H, m)
- 10 ESI-MS (m/e): 535 [$\text{M}+\text{H}$]

実施例472

- 1-アセチル-2-(5-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-3-オール
- 15 ジアステレオマーB

- 実施例471で得られた(1-アセチル-2-(5-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-3-イル)アセテート ジアステレオマーBを用いて、実施例469と同様の方法、これに準じた方法又はこれらと常法とを組み合わせること
- 20 により、表題化合物を得た。

- $^1\text{H NMR}$ (CDCl_3) δ : 1.78–2.25 (5H, m), 3.03–3.10 (3H, m), 3.60–4.00 (2H, m), 4.50–4.68 (1H, m), 5.27–5.45 (1H, m), 7.03–7.73 (5H, m), 7.81–7.96 (3H, m), 8.32–8.45 (1H, m),
- 25 8.60–8.69 (1H, m), 10.51–10.82 (1H, m)
- ESI-MS (m/e): 493 [$\text{M}+\text{H}$]

実施例473

1-(4-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-

2-イル-1H-ベンズイミダゾール-5-イル) オキシ) フェニル) ピペリ
ジン-2-オン

1- (4-ヒドロキシフェニル) ピペリジン-2-オンを用いて、実施例 3
38 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合
5 わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.74-2.62 (13H, m), 3.52-
3.87 (4H, m), 5.18-5.36 (1H, m), 6.71-7.6
4 (7H, m), 7.76-7.90 (1H, m), 8.26-8.41 (1
H, m), 8.56-8.68 (1H, m), 10.98-11.33 (1H,
10 m)

ESI-MS (m/e): 496 [M+H]

実施例 474

6- (1-アセチルピロリジン-2-イル) -5- ((6-フェニルピリジ
15 ン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾー
ル

6-フェニルピリジン-3-オールを用いて、実施例 338 (工程 5) と同
様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
表題化合物を黄色固体として得た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 1.40-2.50 (7H, m), 3.40-4.
00 (2H, m), 5.20-5.60 (1H, m), 6.90-8.00
(11H, m), 8.20-8.45 (1H, m), 8.50-8.70 (2
H, m), 10.60-10.90 (1H, m)

ESI-MS (m/e): 476 [M+H]

25

実施例 475

6- (1-アセチルピロリジン-2-イル) -5- ((6- (2-フルオロ
フェニル) ピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-
ベンズイミダゾール

6 - (2-フルオロフェニル) ピリジン-3-オールを用いて、実施例 3 3
8 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60-2.50 (7H, m), 3.45-4.500 (2H, m), 5.20-5.60 (1H, m), 6.80-8.05 (10H, m), 8.30-8.45 (1H, m), 8.50-8.70 (2H, m), 10.80-11.20 (1H, m)
ESI-MS (m/e): 494 [M+H]

10 実施例 4 7 6

1 - (2 - (6 - (3-フルオロ-4-メタンスルホニル-フェノキシ) - 2-ピリジン-2-イル-3H-ベンゾイミダゾール-5-イル) - ピロリジン-1-イル) - エタノン

(3-フルオロ-4-メタンスルホニル) フェノールを用いて、実施例 3 3
15 8 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.87-2.38 (4H, m), 2.85-3.27 (5H, m), 3.60-3.95 (2H, m), 5.20-5.41 (1H, m), 6.83-7.00 (1H, m), 7.28-7.40 (4H, 20 m), 7.81-7.98 (2H, m), 8.35-8.42 (1H, m), 8.60-8.68 (1H, m)
ESI-MS (m/e): 495 [M+H]

実施例 4 7 7

25 1 - (4 - { [6 - (1-アセチルピロリジン-2-イル) - 2-ピリジン-2-ピリジン-2-イル-1H-ベンゾイミダゾール-5-イル] オキシ} フェニル) ピロリジン-2-オン

1 - (4-ヒドロキシフェニル) ピロリジン-2-オンを用いて、実施例 3 3 8 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ

わせることにより、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80–2.40 (6H, m), 2.62 (2H, m), 3.55–3.95 (4H+1/2H, m), 5.28 (1/2H, m), 6.90–7.10 (3H, m), 7.35 (1H+1/2H, m),
 5 7.45–7.65 (2H+1/2H, m), 7.85 (1H, m), 8.34 (1H, m), 8.61 (1H, m), 10.4–10.8 (1H, br)
 ESI-MS (m/e): 482 [M+H]

実施例 478

10 1-(4-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)フェニル)ピリジン-2(1H)-オン

1-((4-ヒドロキシフェニル)ピリジン-2(1H)-オン)を用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを
 15 組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.72–2.42 (7H, m), 3.48–3.86 (2H, m), 5.15–5.52 (1H, m), 6.19–6.32 (1H, m), 6.61–6.73 (1H, m), 6.80–7.66 (9H, m), 7.77–7.89 (1H, m), 8.32–8.41 (1H, m),
 20 8.52–8.65 (1H, m), 11.07–11.48 (1H, m)
 ESI-MS (m/e): 492 [M+H]

実施例 479

25 5-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)-2,2'-ビピリジン・トリフルオロ酢酸塩

2,2'-ビピリジン-5-オールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

^1H NMR (CD_3OD) δ : 1.80–2.80 (7H, m), 3.60–4.05 (2H, m), 5.20–5.60 (1H, m), 7.50–7.90 (4H, m), 8.00–8.15 (1H, m), 8.15–8.25 (1H, m), 8.30–8.40 (1H, m), 8.45–8.60 (1H, m),
 5 8.60–9.00 (5H, m)
 ESI-MS (m/e): 477 [M+H]

実施例 480

10 N-(2-(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-2-オキソエチル)-メタンスルホンアミド

実施例 162 (工程 7) で得られた 5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール及び N-tert-ブトキシカルボニルグリシンを用いて、実施例 17
 15 1 及び実施例 178 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 1.93–2.14 (3H, m), 2.06–2.27 (1H, m), 2.86 and 2.95 (total 3H, each s), 3.13 (3H, s), 3.43–4.08 (4H, m), 5.20–5.38 (1H, m), 7.20–7.60 (5H, m), 7.93–8.02 (3H, m), 8.23–8.30 (1H, m), 8.74 (1H, br s)

ESI-MS (m/e): 570 [M+H]

25 実施例 481

(2-(2-(6-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-2-オキソエチル)-カルバミン酸 エチルエステル

実施例 162 (工程 7) で得られた 5-(4-メタンスルホニルフェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾールを用いて、実施例 171 及び実施例 178 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

シ) -2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール及びN-tert-ブトキシカルボニル-グリシンを用いて、実施例171及び実施例181と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

- 5 $^1\text{H NMR}$ (CD_3OD) δ : 1.18 and 1.23 (total 3H, each t, J = each 7.1 Hz), 1.93–2.14 (3H, m), 2.22–2.44 (1H, m), 3.12 and 3.13 (total 3H, each s), 3.30–4.13 (6H, m), 5.24–5.33 (1H, m), 7.20–7.60 (5H, m), 7.93–8.01 (3H, m), 8.28 (1H, t, J = 8.2 Hz), 8.73 (1H, br s)
- 10 ESI-MS (m/e): 564 $[\text{M}+\text{H}]$

実施例482

- 15 6-(1-アセチルピロリジン-2-イル)-5-(4-ブロモフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール エナンチオマーA
(工程1)

- N-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド エナンチオマーA及びエナンチオマーBの合成
- 20

- 実施例338 (工程4) で得られたN-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド100mgを光学分割用カラム(CHIRALCEL ODTM 2cm ϕ ×25cmL (ダイセル化学工業社製)、移動相:ヘキサン/エタノール/ジエチルアミン 60/40/0.1、流速:10ml/min)にて光学分割し、
- 25 エナンチオマーA (保持時間:17.8min) 及びエナンチオマーB (保持時間:21.0min) をそれぞれ淡黄色固体として得た。

(工程2)

6-(1-アセチルピロリジン-2-イル)-5-(4-ブロモフェノキシ)-

2-ピリジン-2-イル-1H-ベンズイミダゾール エナンチオマーAの製造

実施例482 (工程1) で得られたN-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド エナンチオマーA、及び4-ブルモフェノールを用いて、実施例338 (工程5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.56-2.41 (7H, m), 3.42-3.90 (2H, m), 5.16-5.51 (1H, m), 6.78-7.66 (7H, m), 7.80-7.93 (1H, m), 8.32-8.44 (1H, m), 8.54-8.67 (1H, m), 11.14-11.65 (1H, m)

ESI-MS (m/e): 479 [M+H]

実施例483

15 6-(1-アセチルピロリジン-2-イル)-5-(4-プロモフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール エナンチオマーB

実施例482 (工程1) で得られたN-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド エナンチオマーB、及び4-ブルモフェノールを用いて、実施例338 (工程5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

ESI-MS (m/e): 479 [M+H]

実施例484

25 6-(1-アセチルピロリジン-2-イル)-5-(6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-オールを用いて、実施例483と同様の方法、これに準じた方法又は

これらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

^1H NMR (CDCl_3) δ : 1.51–2.43 (7H, m), 2.59–2.74 (3H, m), 3.50–3.93 (2H, m), 5.17–5.46 (1H, m), 7.00–7.72 (4H, m), 7.82–8.13 (2H, m), 8.34–8.44 (1H, m), 8.57–8.69 (2H, m), 10.75–11.14 (1H, m)

ESI-MS (m/e): 482 $[\text{M}+\text{H}]$

実施例 485

10 5-(1-アセチル-3-メチルピロリジン-2-イル)-6-(4-(メチルスホニル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

(工程1)

15 N-(3-フルオロ-4-(2-(2-ヒドロキシエチル)アクリロイル)フェニル)ピリジン-2-カルボキサミドの合成

N-(4-ブromo-3-フルオロフェニル)ピリジン-2-カルボキサミド
1.0gのテトラヒドロフラン20ml溶液に、氷冷下、60%水素化ナトリウム136mgを加え、反応液を同温にて15分間攪拌した。反応液を-78度
20 に冷却した後、n-ブチルリチウム(2.66Mヘキサン溶液)1.53mlを滴下し、反応液を同温にて30分間攪拌した。同温にて反応液に3-メチレンジヒドロフラン-2(3H)-オン0.36mlを加え、反応液を同温にて2時間攪拌した後、0度に昇温し、30分間攪拌した。同温にて反応液に飽和重曹水を加え、酢酸エチルにて抽出し、有機層を飽和食塩水にて洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲル
25 クロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=3/1)により精製し、表題化合物を無色油状物質として得た。

(工程2)

N-(4-(1,4-ジヒドロキシ-2-メチルブチル)-3-フルオロフェニル)ピリジン-2-カルボキサミドの合成

N-(3-フルオロ-4-(2-(2-ヒドロキシエチル)アクリロイル)フェニル)ピリジン-2-カルボキサミド 320 mg のメタノール 8 ml 溶液に、水素化ホウ素ナトリウム 150 mg を加え、反応液を室温にて 1 時間攪拌した。反応液に飽和重曹水を加え、クロロホルムにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー（展開溶媒：クロロホルム/メタノール=100/1）により精製し、表題化合物を無色油状物質として得た。

（工程 3）

10 N-(4-(1-アセチル-3-メチルピロリジン-2-イル)-3-フルオロフェニル)ピリジン-2-カルボキサミドの合成

N-(4-(1,4-ジヒドロキシ-2-メチルブチル)-3-フルオロフェニル)ピリジン-2-カルボキサミド 100 mg のクロロホルム 5 ml 溶液に、トリエチルアミン 0.18 ml、メタンスルホニルクロリド 0.07 ml を順次加え、反応液を室温にて 30 分間攪拌した。反応液に飽和重曹水を加え、クロロホルムにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のジメチルホルムアミド 4 ml 溶液に、アジ化ナトリウム 23 mg を加え、反応液を 40 度にて 2 時間攪拌した。反応液を室温に冷却した後、水を加え、酢酸エチルにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のメタノール 5 ml 溶液に、水素化ホウ素ナトリウム 50 mg、硫酸銅・五水和物 5 mg を順次加え、反応液を 40 度にて 15 分間攪拌した。反応液を室温に冷却した後、飽和重曹水を加え、クロロホルムにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のクロロホルム 4 ml 溶液に、トリエチルアミン 0.08 ml、無水酢酸 0.07 ml、N,N-4-ジメチルアミノピリジン 5 mg を順次加え、反応液を室温にて 30 分間攪拌した。反応液に飽和重曹水を加え、クロロホルムにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー（展開溶媒：クロロホルム/メタノール=100/1）により精製し、表題化合物を無色油状物質として得た。

（工程 4）

N-(4-(1-アセチル-3-メチルピロリジン-2-イル)-5-フル
オロ-2-ニトロフェニル)ピリジン-2-カルボキサミドの合成

N-(4-(1-アセチル-3-メチルピロリジン-2-イル)-3-フル
オロフェニル)ピリジン-2-カルボキサミド 70 mg に発煙硝酸 1 ml を加
え、反応液を室温にて 2 時間攪拌した。反応液を氷-飽和重曹水混合溶液に注
ぎ、クロロホルムにて抽出した後、無水硫酸ナトリウムで乾燥した。溶媒を減
圧留去し、得られた残渣を、得られた残渣を分取用薄層クロマトグラフィー
(KieselgelTM 60 F₂₅₄, Art 5744 (メルク社製)、クロロホルム/メタノール=20/1) により精製し、表題化合物を黄色固体として得
た。

(工程 5)

5-(1-アセチル-3-メチルピロリジン-2-イル)-6-(4-(メ
タンスルホニル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダ
ゾールの製造

N-(4-(1-アセチル-3-メチルピロリジン-2-イル)-5-フル
オロ-2-ニトロフェニル)ピリジン-2-カルボキサミド、及び 4-(メタ
ンスルホニル)フェノールを用いて、実施例 338 (工程 5) と同様の方法、これ
に準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白
色固体として得た。

¹H NMR (CDCl₃) δ: 0.81-2.73 (9H, m), 3.03-3.
11 (3H, m), 3.36-3.99 (2H, m), 4.65-5.43
(1H, m), 7.00-7.75 (5H,), 7.81-7.79 (3H,
m), 8.32-8.45 (1H, m), 8.60-8.68 (1H, m),
10.51-10.82 (1H, br)

ESI-MS (m/e): 491 [M+H]

実施例 486

6 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) - 3, 4 - ジヒドロナフタレン - 1 (2 H) - オン

- 5 実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.00 - 3.00 (13 H, m), 3.40 - 3.95 (2 H, m), 5.00 - 5.50 (1 H, m), 6.60 - 7.80 (5 H, m), 7.80 - 8.20 (2 H, m), 8.30 - 8.50 (1 H, m), 8.50 - 8.80 (1 H, m), 10.80 - 11.20 (1 H, m)

ESI-MS (m/e): 467 [M+H]

実施例 487

- 15 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (1 H - イミダゾール - 1 - イル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール

- 20 4 - (1 H - イミダゾール - 1 - イル) フェノールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.00 - 2.50 (7 H, m), 3.50 - 4.50 (2 H, m), 5.20 - 6.00 (1 H, m), 6.80 - 8.80 (13 H, m)

ESI-MS (m/e): 465 [M+H]

25

実施例 488

6 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) - 1 - メチル - [1, 2, 3, 4] - テトラヒドロナフタレン - 1 - オール

実施例 486 で得られた 6-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)-3,4-ジヒドロナフタレン-1(2H)-オン 7mg のテトラヒドロフラン 0.5ml 溶液に、氷冷下、臭化メチルマグネシウム (5.0M テトラヒドロフラン溶液) 0.050ml を加え、反応液を 0 度にて 30 分間攪拌した。反応液を、クロロホルムにて希釈し、飽和塩化アンモニウム水溶液にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (Kieselgel TM60F254, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を無色油状物質として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10–2.80 (16H, m), 3.50–4.00 (2H, m), 5.10–5.50 (1H, m), 6.60–7.90 (7H, m), 8.30–8.50 (1H, m), 8.50–7.0 (1H, m)

ESI-MS (m/e): 465 [M+H]

実施例 489

6-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)-[1,2,3,4]-テトラヒドロナフタレン-1-オール

実施例 486 で得られた 6-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)-3,4-ジヒドロナフタレン-1(2H)-オン 7mg のテトラヒドロフラン 0.5ml 溶液に、氷冷下水素化ホウ素ナトリウム 5mg を加え、反応液を室温にて 30 分間攪拌した。反応液をクロロホルムにて希釈し、飽和塩化アンモニウム水溶液にて洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (Kieselgel TM60F254, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を無色油状物質として得た。

^1H NMR (CDCl_3) δ : 1.00–2.50 (14H, m), 4.00–6.00 (3H, m), 6.80–8.50 (9H, m)
ESI-MS (m/e): 469 [M+H]

5 実施例490

5-(1-アセチル-3-フルオロピロリジン-2-イル)-6-(4-(メ
タンスルホニル)フェノキシ)-2-ピリジン-2-イル-1 H-ベンズイミダ
ゾール ジアステレオマーA

(工程1)

- 10 エチル (2 Z) -4-((t-ブチル (ジメチル) シリル)オキシ)-2-フルオ
ロプト-2-エノエートの合成

(ジエトキシホスホリル) (フルオロ) 酢酸エチル 2.0 g のテトラヒドロ
フラン 40 ml 溶液を -78 度に冷却した後、n-ブチルリチウム (2.66
M ヘキサン溶液) 3.4 ml を滴下し、反応液を同温にて 15 分間攪拌した。

- 15 反応液に ((t-ブチル (ジメチル) シリル)オキシ)アセトアルデヒド 2.1 ml
1 を加え、反応液を同温にて 2 時間攪拌した。同温にて反応溶液に飽和重曹水
を加え、室温に昇温した後、酢酸エチルにて抽出した。無水硫酸ナトリウムに
て乾燥後、溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー
(展開溶媒: ヘキサン/酢酸エチル = 50/1) により精製し、表題化合物を
20 無色油状物質として得た。

(工程2)

N-(4-((2 Z) -4-((t-ブチル (ジメチル) シリル)オキシ)-2-
フルオロプト-2-エノイル) -3-フルオロフェニル)ピリジン-2-カルボ
キサアミドの合成

- 25 N-(4-ブロモ-3-フルオロフェニル)ピリジン-2-カルボキサアミド
1.0 g のテトラヒドロフラン 40 ml 溶液に、氷冷下、60%水素化ナトリ
ウム 136 mg を加え、反応液を同温にて 20 分間攪拌した。反応液を -78
度に冷却した後、n-ブチルリチウム (2.66 M ヘキサン溶液) 1.53 ml
1 を滴下し、反応液を同温にて 20 分間攪拌した。同温にて反応液にエチル

(2 Z) - 4 - ((t - ブチル (ジメチル) シリル) オキシ) - 2 - フルオロブト -
2 - エノエート 1. 07 g を加え、反応液を同温にて 4 時間攪拌した。同温に
て反応液に飽和重曹水を加え、室温に昇温した後、酢酸エチルにて抽出し、有
機層を飽和食塩水にて洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留
5 去し、得られた残渣をシリカゲルクロマトグラフィー (展開溶媒: ヘキサン/
酢酸エチル = 3 / 1) により精製し、表題化合物を無色油状物質として得た。

(工程 3)

N - (4 - (4 - ((t - ブチル (ジメチル) シリル) オキシ) - 2 - フルオロ -
1 - ヒドロキシブチル) - 3 - フルオロフェニル) ピリジン - 2 - カルボキサ
10 ミド

N - (4 - ((2 Z) - 4 - ((t - ブチル (ジメチル) シリル) オキシ) - 2 -
フルオロブト - 2 - エノイル) - 3 - フルオロフェニル) ピリジン - 2 - カルボ
キサアミド 300 mg のメタノール 20 ml 溶液に、10% パラジウム - 炭素
触媒 100 mg を加え、水素雰囲気下、反応液を室温にて 4 時間攪拌した。触
15 媒を濾過後、溶媒を減圧留去し、得られた残渣のメタノール 4 ml 溶液に、水
素化ホウ素ナトリウム 50 mg を加え、反応液を室温にて 1 時間攪拌した。反
応液に飽和重曹水を加え、クロロホルムにて抽出し、無水硫酸ナトリウムで乾
燥した。溶媒を減圧留去し、得られた残渣をシリカゲルクロマトグラフィー
(展開溶媒: クロロホルム / メタノール = 100 / 1) により精製し、表題化
20 合物を無色油状物質として得た。

(工程 4)

N - (4 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 3 - フル
オロフェニル) ピリジン - 2 - カルボキサアミド ジアステレオマー A、及びジ
アステレオマー B の合成

25 N - (4 - (4 - ((t - ブチル (ジメチル) シリル) オキシ) - 2 - フルオ
ロ - 1 - ヒドロキシブチル) - 3 - フルオロフェニル) ピリジン - 2 - カルボキ
サアミド 100 mg のクロロホルム 5 ml 溶液に、トリエチルアミン 46 mg、
メタンスルホンクロリド 39 mg を順次加え、反応液を室温にて 30 分間攪
拌した。反応液に飽和重曹水を加え、クロロホルムにて抽出し、無水硫酸ナト

リウムで乾燥した。溶媒を減圧留去し、得られた残渣のジメチルホルムアミド 4 ml 溶液に、アジ化ナトリウム 22 mg を加え、反応液を 40 度にて 2 時間攪拌した。反応液を冷却した後、水を加え、酢酸エチルにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のテトラヒドロフラン 4 ml 溶液にテトラブチルアンモニウムフロリド (1.0 M テトラヒドロフラン溶液) 0.3 ml 加え、反応液を室温にて 1 時間攪拌した。反応液に、水を加え、酢酸エチルにて抽出し、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣のクロロホルム 5 ml 溶液に、トリエチルアミン 46 mg、メタンスルホニルクロリド 39 mg を順次加え、反応液を室温にて 30 分間攪拌した。反応液に、飽和重曹水を加え、酢酸エチルにて抽出し、無水硫酸ナトリウムにて乾燥した。溶媒を減圧留去し、得られた残渣のメタノール 4 ml 溶液に硫酸銅・五水和物 10 mg、水素化ホウ素ナトリウム 50 mg を順次加え、反応液を 40 度にて 1 時間攪拌した。反応液を冷却した後、飽和重曹水を加え、クロロホルムで抽出し、無水硫酸ナトリウムにて乾燥した。溶媒を減圧留去し、得られた残渣のクロロホルム 4 ml 溶液に、トリエチルアミン 46 mg、無水酢酸 35 mg、N, N-4-ジメチルアミノピリジン 5 mg を順次加え、反応液を室温にて 30 分間攪拌した。溶媒を減圧留去し、得られた残渣を、分取用薄層クロマトグラフィー(クロロホルム/メタノール=30/1)により精製し、表題化合物のジアステレオマーA、及びジアステレオマーB をそれぞれ無色油状物質として得た。

(工程5)

5-(1-アセチル-3-フルオロピロリジン-2-イル)-6-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1 H-ベンズイミダゾール ジアステレオマーA の製造

25 N-(4-(1-アセチル-3-フルオロピロリジン-2-イル)-3-フルオロフェニル)ピリジン-2-カルボキサミド ジアステレオマーA 18 mg に、発煙硝酸 0.5 ml を加え、反応液を室温にて 10 分間攪拌した。反応液を氷-飽和重曹水混合溶液中に注ぎ、クロロホルムにて抽出した後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、粗生成物を得た。得られた組成生

物、及び4-(メタンスルホニル)フェノールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

¹HNMR (CDCl₃) δ: 1.85-2.40 (5H, m), 3.06 and 3.09 (3H, s), 3.79-4.08 (2H, m), 4.96-5.62 (2H, m), 7.05-7.70 (5H, m), 7.83-7.99 (3H, m), 8.34-8.43 (1H, m), 8.61-8.69 (1H, m), 10.58-10.84 (1H, m)
ESI-MS (m/e): 495 [M+H]

10

実施例491

6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-5-(4-(2-チエニル)フェノキシ)-1H-ベンズイミダゾール

4-(2-チエニル)フェノールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

¹HNMR (CDCl₃) δ: 1.05-2.45 (7H, m), 3.40-4.00 (2H, m), 5.10-5.60 (1H, m), 6.80-8.00 (1.1H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m)
ESI-MS (m/e): 481 [M+H]

20

実施例492

2-(4-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)フェニル)-1H-イソインドール-1,3(2H)-ジオン

25

2-(4-ヒドロキシフェニル)-1H-イソインドール-1,3(2H)-ジオンを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体と

して得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.05–2.40 (7H, m), 3.40–4.05 (2H, m), 5.05–5.60 (1H, m), 6.80–8.20 (12H, m), 8.30–8.70 (2H, m)

5 ESI-MS (m/e): 544 $[\text{M}+\text{H}]$

実施例 493

5 – (1-アセチル-3-フルオロピロリジン-2-イル) – 6 – (4-(メ
タンスルホニル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダ
10 ザール ジアステレオマーB

実施例 490 (工程 4) で得られた N-(4-(1-アセチル-3-フルオ
ロピロリジン-2-イル)-3-フルオロフェニル)ピリジン-2-カルボキシ
アミド ジアステレオマーB を用いて、実施例 490 (工程 5) と同様の方法、
これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物

15 を淡黄色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.80–2.45 (5H, m), 3.05 a
nd 3.08 (3H, s), 3.61–4.31 (2H, m), 5.08–
5.54 (2H, m), 7.03–7.80 (5H, m), 7.81–7.9
7 (3H, m), 8.33–8.43 (1H, m), 8.60–8.68 (1

20 H, m), 10.52–10.75 (1H, m)

ESI-MS (m/e): 495 $[\text{M}+\text{H}]$

実施例 494

6 – (1-アセチルピロリジン-2-イル) – 5 – (4-(5-メチル-1H
25 –テトラゾール-1-イル)フェノキシ)-2-ピリジン-2-イル-1H-
ベンズイミダゾール

4-(5-メチル-1H-テトラゾール-1-イル)フェノールを用いて、
実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法と
を組み合わせることにより、表題化合物を白色固体として得た。

^1H NMR (CD_3OD) δ : 1.91 and 2.15 (total 3H, each s), 1.97–2.20 (3H, m), 2.22–2.58 (1H, m), 2.63 and 2.64 (total 3H, each s), 3.62–4.00 (2H, m), 5.34–5.42 (1H, m), 7.2
 5 2–7.68 (7H, m), 7.94–8.05 (1H, m), 8.30 (1H, t, $J=7.8\text{Hz}$), 8.76 (1H, brs)
 ESI-MS (m/e): 481 $[\text{M}+\text{H}]$

実施例 495

10 エチル 5-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-カルボキシレート

エチル 5-ヒドロキシピリジン-2-カルボキシレートを用いて、実施例
 338 (工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み
 15 合わせることで、表題化合物を黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.30–1.50 (3H, m), 1.50–2.50 (7H, m), 3.50–3.90 (2H, m), 4.35–4.60 (2H, m), 5.10–5.45 (1H, m), 6.90–7.70 (4H, m), 7.80–7.95 (1H, m), 8.00–8.20 (1H, m),
 20 8.30–8.80 (3H, m), 10.60–11.20 (1H, m)
 ESI-MS (m/e): 472 $[\text{M}+\text{H}]$

実施例 496

25 6-(1-アセチルピロリジン-2-イル)-5-(4-ピラジン-2-イルフェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-ピラジン-2-イルフェノールを用いて、実施例338 (工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 0.80–2.40 (7H, m), 3.60–3.90 (2H, m), 5.20–5.60 (1H, m), 6.80–8.05 (8H, m), 8.30–8.80 (4H, m), 8.90–9.10 (1H, m), 10.40–10.80 (1H, m)

5 ESI-MS (m/e): 477 [M+H]

実施例 497

6-(1-アセチルピロリジン-2-イル)-5-(1H-インドール-5-イルオキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

10 1H-インドール-5-オールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.20–2.40 (7H, m), 3.60–4.00 (2H, m), 5.20–5.60 (1H, m), 6.40–6.60

15 (1H, m), 6.80–8.00 (7H, m), 8.20–8.50 (2H, m), 8.50–8.80 (1H, m)

ESI-MS (m/e): 438 [M+H]

実施例 498

20 2-(2-(5-(2'-フルオロピフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-1-イル)-2-オキソエチル)メチルアミン

(工程 1)

(3-フルオロ-4-ピロリジン-2-イルフェニル)アミン二塩酸塩の合成

25 実施例 338 (工程 2) で得られた、2-(4-アミノ-2-フルオロフェニル)-ピロリジン-1-カルボン酸 t-ブチルエステル 19 g の酢酸エチル 50 ml とメタノール 50 ml 混合溶液に、氷冷下 4 規定塩酸-ジオキサン溶液 100 ml を加え、反応液を室温にて一終夜攪拌した。溶媒を減圧留去し、表題化合物を白色固体として得た。

(工程 2)

2, 2, 2-トリフルオロ-N-(3-フルオロ-4-(1-(トリフルオロアセチル)ピロリジン-2-イル)フェニル)アセタミドの合成

(3-フルオロ-4-ピロリジン-2-イルフェニル)アミン二塩酸塩 20
5 g のクロロホルム 200 ml 懸濁液に、氷冷下ピリジン 39 ml 及びトリフル
オロ酢酸無水物 24 ml を順次加え、反応液を室温にて 30 分間攪拌した。反
応液を酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグ
ネシウムで乾燥した。溶媒を減圧留去し、表題化合物を褐色油状物質として得
た。

10 (工程 3)

2, 2, 2-トリフルオロ-N-(5-フルオロ-2-ニトロ-4-(1-(トリフルオロアセチル)ピロリジン-2-イル)フェニル)アセタミドの合
成

2, 2, 2-トリフルオロ-N-(3-フルオロ-4-(1-(トリフルオ
15 ロアセチル)ピロリジン-2-イル)フェニル)アセタミド 28 g に、氷冷下
発煙硝酸 100 ml を加え、反応液を室温にて 1 時間攪拌した。反応液に氷水
を加え希釈後、酢酸エチルにて抽出し、飽和食塩水にて洗浄後、無水硫酸マグ
ネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムク
ロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=10/1)により精製
20 し、表題化合物を黄色油状物質として得た。

(工程 4)

t-ブチル 2-(4-アミノ-2-フルオロ-5-ニトロフェニル)ピロリ
ジン-1-カルボキシレート

2, 2, 2-トリフルオロ-N-(5-フルオロ-2-ニトロ-4-(1-(トリフルオロアセチル)ピロリジン-2-イル)フェニル)アセタミド 29
25 g のテトラヒドロフラン 150 ml 溶液に、氷冷下 1 規定水酸化ナトリウム水
溶液 150 ml を加え、反応液を室温にて 5 時間攪拌した。さらに反応液に二
炭酸ジ t-ブチル 23 ml を加え、反応液を 30 分攪拌した。反応液を酢酸エ
チルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾

燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝5／1）にて精製し、表題化合物を黄色固体として得た。

（工程5）

- 5 t-ブチル 2-（4-アミノ-2-（（2'-フルオロビフェニル-4-イル）オキシ）-5-ニトロフェニル）ピロリジン-1-カルボキシレート

- 10 t-ブチル 2-（4-アミノ-2-フルオロ-5-ニトロフェニル）ピロリジン-1-カルボキシレート 288 mg のN, N-ジメチルホルムアミド 3 ml 溶液に、2'-フルオロビフェニル-4-オール 200 mg 及び炭酸カリウム 184 mg を加え、反応液を80度にて一終夜攪拌した。反応液を酢酸エチルにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝5／1）にて精製し、表題化合物
- 15 を黄色固体として得た。

（工程6）

t-ブチル 2-（4, 5-ジアミノ-2-（（2'-フルオロビフェニル-4-イル）オキシ）フェニル）ピロリジン-1-カルボキシレートの合成

- 20 t-ブチル 2-（4-アミノ-2-（（2'-フルオロビフェニル-4-イル）オキシ）-5-ニトロフェニル）ピロリジン-1-カルボキシレート 410 mg のメタノール 5 ml 溶液に、展開ラネーニッケル触媒 1 ml を加え、反応液を水素雰囲気下、室温にて一日攪拌した。触媒をセライトにて濾去後、溶媒を減圧留去し、残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／1）にて精製し、表題化合物を褐色油状物質として得た。
- 25

（工程7）

5-（（2'-フルオロビフェニル-4-イル）オキシ）-2-ピロリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾールの合成

t-ブチル 2-（4, 5-ジアミノ-2-（（2'-フルオロビフェニル

ル-4-イル) オキシ) フェニル) ピロリジン-1-カルボキシレート 255 mg のメタノール 5 ml 溶液に、N-((1E)-ピリジン-2-イルメチレン) アニリン (1M メタノール溶液) 1.6 ml を加え、反応液を 90 度にて 1 日攪拌した。反応液を酢酸エチルにて希釈し、水、飽和食塩水にて順次洗
 5 浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣 332 mg に 4 規定塩酸-ジオキサン溶液 5 ml を加え、反応液を室温にて 3 時間攪拌した。溶媒を減圧留去し、飽和重曹水にて希釈後、クロロホルムにて抽出した。有機層を飽和食塩水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣シリカゲルカラムクロマトグラフィー (展開
 10 溶媒: クロロホルム/メタノール/アンモニア水溶液 = 20/1/0.1) にて精製し、表題化合物を黄色油状物質として得た。

(工程 8)

(2-(2-(5-((2'-フルオロピフェニル-4-イル) オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル) ピロリジン-1-イル)-2-オキソエチル) メチルアミンの製造
 15 5-((2'-フルオロピフェニル-4-イル) オキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール 37 mg のピリジン 1 ml 溶液に、N-(t-ブトキシカルボニル)-N-メチルグリシン 19 mg、1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミ
 20 ド・一塩酸塩 24 mg を順次加え、反応液を室温にて 3 時間攪拌した。反応液に 4 規定塩酸-ジオキサン溶液 2 ml を加え、反応液を室温にて 1 時間攪拌した。反応液を、クロロホルムにて希釈し、飽和重曹水にて塩基性とした後、有機層を飽和食塩水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ク
 25 ロロホルム/メタノール = 10/1) にて精製し、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.60-2.60 (6H, m), 2.80-3.05 (1H, m), 3.10-4.00 (4H, m), 5.20-5.60 (1H, m), 6.95-7.70 (11H, m), 7.75-7.95 (1

H, m), 8.30–8.50 (1H, m), 8.50–8.70 (1H, m)

ESI-MS (m/e) : 522 [M+H]

5 実施例499

6-(1-アセチルピロリジン-2-イル)-5-(6-(5-メチル-[1, 3, 4]-オキサジアゾール-2-イル)ピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 6-(5-メチル-[1, 3, 4]-オキサジアゾール-2-イル)ピリジン-3-オールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

- ¹HNMR (CDCl₃) δ : 1.40–2.40 (7H, m), 2.50–2.80 (3H, m), 3.50–3.95 (2H, m), 5.05–5.50 (1H, m), 6.80–7.80 (4H, m), 7.80–8.00 (1H, m), 8.05–8.30 (1H, m), 8.30–8.50 (1H, m), 8.50–8.80 (2H, m), 10.50–11.00 (1H, m)

ESI-MS (m/e) : 482 [M+H]

20 実施例500

6-(1-アセチルピロリジン-2-イル)-5-(6-(1, 3, 4-オキサジアゾール-2-イル)ピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 6-(1, 3, 4-オキサジアゾール-2-イル)ピリジン-3-オールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

¹HNMR (CDCl₃) δ : 1.40–2.40 (7H, m), 3.50–3.95 (2H, m), 5.05–5.50 (1H, m), 6.80–7.80

(4H, m), 7.80–8.00 (1H, m), 8.05–8.80 (5H, m), 10.50–11.00 (1H, m)

ESI-MS (m/e) : 468 [M+H]

5 実施例501

6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-5-(4-ピリミジン-2-イルフェノキシ)-1H-ベンズイミダゾール

4-ピリミジン-2-イルフェノールを用いて、実施例338 (工程5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、

10 表題化合物を白色固体として得た。

¹HNMR (CD₃OD) δ : 1.90 and 2.13 (total 3H, each s), 1.94–2.53 (4H, m), 3.62–3.80 (1H, m), 3.80–4.00 (1H, m), 5.38–5.46 (1H, m), 7.16–7.56 (6H, m), 7.95–8.04 (1H, m), 8.

15 24–8.33 (1H, m), 8.46 (2H, d, J=9.0Hz), 8.70–8.79 (1H, m), 8.83–8.85 (2H, m)

ESI-MS (m/e) : 477 [M+H]

実施例502

20 1-(5-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-イル)メチル)ピロリジン-2,5-ジオン

1-(5-ヒドロキシピリジン-2-イル)メチル)ピロリジン-2,5-ジオンを用いて、実施例338 (工程5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1.80–2.46 (7H, m), 2.74–2.86 (4H, m), 3.53–3.90 (2H, m), 4.76–4.87 (2H, m), 5.18–5.48 (1H, m), 6.76–7.67 (5H,

m), 7.80-7.91 (1H, m), 8.28-8.44 (2H, m),
 8.57-8.67 (1H, m), 11.07-11.41 (1H, m)
 ESI-MS (m/e) : 511 [M+H]

5 実施例503

6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-5-
(6-(5-(トリフルオロメチル)-[1, 2, 4]-オキサジアゾール
-3-イル)ピリジン-3-イル)オキシ)-1H-ベンズイミダゾール

- 10 6-(5-(トリフルオロメチル)-[1, 2, 4]-オキサジアゾール-
 3-イル)ピリジン-3-オールを用いて、実施例338(工程5)と同様の
 方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
 化合物を白色固体として得た。

¹HNMR (CD₃OD) δ : 1.89-2.54 (7H, m), 3.84-4.
 15 01 (2H, m), 5.32-5.42 (1H, m), 7.20-7.80 (
 4H, m), 7.98-8.03 (1H, m), 8.24-8.37 (2H,
 m), 8.60-8.65 (1H, m), 8.73-8.80 (1H, m)
 ESI-MS (m/e) : 536 [M+H]

20 実施例504

6-(1-アセチルピロリジン-2-イル)-5-(6-クロロピリジン-
3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 6-クロロピリジン-3-オールを用いて、実施例338(工程5)と同様
 の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表
 25 題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-3.
 95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70
 (5H, m), 7.80-8.50 (3H, m), 8.50-8.70 (1H,
 m), 10.60-11.00 (1H, m)

ESI-MS (m/e) : 434 [M+H]

実施例505

5 6-(1-アセチルピロリジン-2-イル)-5-(6-プロモピリジン-3-イル)オキシ-2-ピリジン-2-イル-1H-ベンズイミダゾール

6-プロモピリジン-3-オールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H, m), 7.70-8.00 (1H, m), 8.05-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m)

ESI-MS (m/e) : 478, 480 [M+H]

15

実施例506

6-(1-アセチルピロリジン-2-イル)-5-(6-メトキシピリジン-3-イル)オキシ-2-ピリジン-2-イル-1H-ベンズイミダゾール

20 6-メトキシピリジン-3-オールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色固体として得た。

¹HNMR (CDCl₃) δ : 1.60-2.60 (7H, m), 3.50-4.10 (5H, m), 5.10-5.70 (1H, m), 6.60-7.70 (5H, m), 7.70-7.95 (1H, m), 7.95-8.10 (1H, m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m)

ESI-MS (m/e) : 430 [M+H]

25

実施例 507

5 - ((2' -フルオロビフェニル - 4 - イル) オキシ) - 6 - (1 - (メタ
ンスルホニル) ピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1H - ベ
ンズイミダゾール

- 5 実施例 498 (工程 7) で得られた 5 - ((2' -フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 6 - ピロリジン - 2 - イル - 1H - ベンズイミダゾールを用いて、実施例 178 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色油状物質として得た。
- 10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.80 - 2.20 (3H, m), 2.20 - 2.50 (1H, m), 2.70 - 3.00 (3H, m), 3.40 - 3.80 (2H, m), 5.10 - 5.40 (1H, m), 6.90 - 8.10 (12H, m), 8.30 - 8.50 (1H, m), 8.50 - 8.70 (1H, m), 10.50 - 10.80 (1H, m)
- 15 ESI-MS (m/e) : 529 [M+H]

実施例 508

メチル 2 - (5 - ((2' -フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダゾール - 6 - イル) ピロリジン - 1 - カルボキシレート

- 20 実施例 498 (工程 7) で得られた 5 - ((2' -フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 6 - ピロリジン - 2 - イル - 1H - ベンズイミダゾールを用いて、実施例 181 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を無色油状物質として得た。
- $^1\text{H-NMR}$ (CDCl_3) δ : 1.80 - 2.20 (3H, m), 2.20 - 2.50 (1H, m), 3.40 - 3.80 (5H, m), 5.10 - 5.40 (1H, m), 6.90 - 8.10 (12H, m), 8.30 - 8.50 (1

H, m), 8.50–8.70 (1H, m), 10.50–10.80 (1H, m)

ESI-MS (m/e) : 509 [M+H]

5 実施例509

2-(5-((2'-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)-N,N-ジメチルピロリジン-1-カルボキサミド

10 実施例498(工程7)で得られた5-((2'-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾールを用いて、実施例336(工程1)及び(工程2)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1.60–2.20 (3H, m), 2.20–2.50 (1H, m), 2.72 (3H, s), 2.84 (3H, s), 3.40–3.80 (2H, m), 5.10–5.40 (1H, m), 6.90–8.10 (12H, m), 8.30–8.50 (1H, m), 8.50–8.70 (1H, m), 10.50–10.80 (1H, m)

ESI-MS (m/e) : 522 [M+H]

20

実施例510

1-((5-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-イル)メチル)ピロリジン-2-オン

25 1-((5-ヒドロキシピリジン-2-イル)メチル)ピロリジン-2-オンを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

¹HNMR (CDCl₃) δ : 1.80–2.57 (11H, m), 3.33–3.89 (4H, m), 4.48–4.64 (2H, m), 5.20–5.5

1 (1H, m), 6.77-7.67 (5H, m), 7.77-7.90 (1H, m), 8.27-8.42 (2H, m), 8.56-8.66 (1H, m), 11.16-11.53 (1H, m)
ESI-MS (m/e) : 497 [M+H]

5

実施例511

6-(1-アセチルピロリジン-2-イル)-5-(4-(3-メチル-1H-[1,2,4]-トリアゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 10 4-(3-メチル-1H-[1,2,4]-トリアゾール-5-イル)フェノールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

¹HNMR (CDCl₃) δ: 1.76-2.82 (10H, m), 3.50-3.90 (2H, m), 5.13-5.59 (1H, m), 6.64-8.04 (8H, m), 8.23-8.64 (2H, m)
ESI-MS (m/e) : 480 [M+H]

15

実施例512

- 20 6-(1-(ジフルオロアセチル)ピロリジン-2-イル)-5-(2-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

ジフルオロ酢酸を用いて、実施例498(工程8)同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

25

¹HNMR (CDCl₃) δ: 1.80-2.50 (4H, m), 3.60-4.20 (2H, m), 5.20-6.20 (2H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m)

ESI-MS (m/e) : 529 [M+H]

実施例 513

5 2-(2-(5-(2'-フルオロピフェニル-4-イル)オキシ)-2-
ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-
1-イル)-2-オキソエチル アセテート

アセトキシ酢酸を用いて、実施例 498 (工程 8) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

10 ¹H NMR (CDCl₃) δ : 1.60-2.40 (7H, m), 3.40-4.00 (2H, m), 4.05-4.80 (2H, m), 5.10-5.60 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m)

15 ESI-MS (m/e) : 551 [M+H]

実施例 514

20 (5-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-
イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-イル)
メタノール

実施例 495 で得られたエチル 5-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-カルボキシレート 90 mg のテトラヒドロフラン 2 ml 溶液に、氷冷下、水素化リチウムアルミニウム 20 mg を加え、反応液
25 を 0 度にて 30 分間攪拌した。反応液をクロロホルムにて希釈し、飽和塩化アンモニウム水溶液、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィ (Kieselgel TM 60 F254, Art 5744 (メルク社

製)、クロロホルム/メタノール=10/1)にて精製し、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60–2.60 (7H, m), 3.50–4.00 (2H, m), 4.70–4.85 (2H, m), 5.10–5.60 (1H, m), 6.80–7.70 (5H, m), 7.70–7.95 (1H, m), 8.30–8.50 (2H, m), 8.50–8.70 (1H, m)
ESI-MS (m/e): 430 [M+H]

実施例515

10 2-(2-(5-(2'-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-1-イル)-2-オキソエタノール

実施例513で得られた2-(2-(5-(2'-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-1-イル)-2-オキソエチル アセテート11mg
15 のメタノール0.5ml溶液に、炭酸カリウム10mgを加え、反応液を室温にて1日攪拌した。反応液をクロロホルムにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー(Kieselgel TM60F254, Ar
20 t 5744 (メルク社製)、クロロホルム/メタノール=10/1)にて精製し、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.40–2.50 (4H, m), 3.40–4.20 (4H, m), 5.05–5.70 (1H, m), 6.90–8.10 (12H, m), 8.30–8.50 (1H, m), 8.50–8.70 (1H, m), 10.50–10.80 (1H, m)
25 ESI-MS (m/e): 509 [M+H]

実施例516

6-(1-アセチルピロリジン-2-イル)-5-((6-(フルオロメチル)ピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例 514 で得られた (5-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-イル)メタノール 17mg のクロロホルム 1ml 溶液に、氷冷下ビス(2-メトキシエチル)アミノサルファートリフロライド 0.050ml を加え、反応液を 0 度にて 2 時間攪拌した。反応液をクロロホルムにて希釈し、飽和重曹水、飽和食塩水にて順次洗浄後、無水硫酸ナトリウムで乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (Kieselgel TM60F254, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を微黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.60 (3H, m), 6.80-7.70 (5H, m), 7.70-7.95 (1H, m), 8.30-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m)

ESI-MS (m/e): 432 [$M+H$]

20

実施例 517

6-(1-アセチルピロリジン-2-イル)-5-((6-(3-メチル-[1, 2, 4]-オキサジアゾール-5-イル)ピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

6-(3-メチル[1, 2, 4]-オキサジアゾール-5-イル)ピリジン-3-オールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.65-2.57 (10H, m), 3.48-

3. 93 (5H, m), 5. 17-5. 52 (1H, m), 6. 82-7. 6
7 (7H, m), 7. 80-7. 91 (1H, m), 8. 34-8. 44 (1
H, m), 8. 57-8. 67 (1H, m), 11. 32-11. 68 (1H,
m)

5 ESI-MS (m/e) : 482 [M+H]

実施例 518

6-(1-アセチルピロリジン-2-イル)-5-(4-(1-メチル-1H-
-テトラゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-1H-
10 ベンズイミダゾール

4-(1-メチル-1H-テトラゾール-5-イル)フェノールを用いて、
実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法と
を組み合わせることにより、表題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1. 83-2. 40 (7H, m), 3. 58-3.
15 90 (2H, m), 4. 15 and 4. 19 (total 3H, each
s), 5. 16-5. 48 (1H, m), 6. 93-7. 78 (7H, m),
7. 80-7. 91 (1H, m), 8. 34-8. 42 (1H, m), 8. 5
6-8. 65 (1H, m)

ESI-MS (m/e) : 481 [M+H]

20

実施例 519

5-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イ
ル-1H-ベンズイミダゾール-5-イル) オキシ) -N-メチルピリジン-
2-カルボキサミド

25 5-ヒドロキシ-N-メチルピリジン-2-カルボキサミドを用いて、実施
例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組
み合わせるることにより、表題化合物を淡黄色固体として得た。

¹HNMR (CDCl₃) δ : 1. 60-2. 50 (7H, m), 2. 90-3.
10 (3H, m), 3. 50-4. 00 (2H, m), 5. 05-5. 50

(1H, m), 6.80–7.70 (3H, m), 7.70–8.00 (2H, m), 8.10–8.50 (3H, m), 8.50–8.70 (1H, m)

ESI-MS (m/e) : 457 [M+H]

5 実施例520

3-(5-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-イル)-1,3-オキサゾリジン-2-オン

- 3-(5-ヒドロキシピリジン-2-イル)-1,3-オキサゾリジン-2-オンを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- ¹HNMR (CDCl₃) δ : 1.60–2.50 (7H, m), 3.50–4.00 (2H, m), 4.10–4.35 (2H, m), 4.40–4.60 (2H, m), 5.20–5.60 (1H, m), 6.80–7.70 (4H, m), 7.70–8.00 (1H, m), 8.10–8.50 (3H, m), 8.50–8.70 (1H, m), 10.70–11.10 (1H, m)
- ESI-MS (m/e) : 485 [M+H]

20 実施例521

6-(1-アセチルピロリジン-2-イル)-5-(6-メチルピリジン-3-イルスルファニル)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 6-メチルピリジン-3-チオールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

¹HNMR (CDCl₃) δ : 1.20–2.50 (10H, m), 3.50–4.00 (2H, m), 5.20–5.60 (1H, m), 6.80–8.00 (6H, m), 8.20–8.70 (3H, m)

ESI-MS (m/e) : 430 [M+H]

実施例 522

5 5-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ニコチン酸メチルエステル

5-ヒドロキシニコチン酸メチルエステルを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

10 ^1H NMR (CD_3OD) δ : 1.89 and 2.14 (total 3H, each s), 1.96-2.20 (3H, m), 2.32-2.54 (1H, m), 3.63-3.90 (2H, m), 3.93 (3H, s), 5.37-5.41 (1H, m), 7.20-7.57 (3H, m), 7.92-8.03 (2H, m), 8.30 (1H, t, $J=8.4\text{Hz}$), 8.65-8.67 (1H, m), 8.74-8.78 (1H, m), 8.89-8.92 (1H, m)

ESI-MS (m/e) : 458 [M+H]

実施例 523

20 6-(1-アセチルピロリジン-2-イル)-5-(6-(メチルチオ)ピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

25 6-メチルチオピリジン-3-オールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

^1H NMR (CDCl_3) δ : 1.60-2.70 (10H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.10 (6H, m), 8.20-8.50 (2H, m), 8.50-8.70 (1H, m), 10.70-11.10 (1H, m)

ESI-MS (m/e) : 446 [M+H]

実施例 524

6-(1-アセチルピロリジン-2-イル)-5-(4-(1,3-ジメチル-1H-[1,2,4]-トリアゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-(1,3-ジメチル-1H-[1,2,4]-トリアゾール-5-イル)フェノールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.79-2.25 (10H, m), 3.50-3.90 (5H, m), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m), 10.82-11.08 (1H, m)

ESI-MS (m/e) : 494 [M+H]

実施例 525

6-(1-アセチルピロリジン-2-イル)-5-(4-(1,5-ジメチル-1H-[1,2,4]-トリアゾール-3-イル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-(1,5-ジメチル-1H-[1,2,4]-トリアゾール-3-イル)フェノールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.79-2.53 (10H, m), 3.50-3.90 (5H, m), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m)

m), 10.82-11.08 (1H, m)

ESI-MS (m/e) : 494 [M+H]

実施例 526

- 5 6-(1-アセチルピロリジン-2-イル)-5-((2'-フルオロビフェニル-4-イル)オキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

- 10 実施例 338 (工程 2) で得られた 2-(4-アミノ-2-フルオロフェニル)-ピロリジン-1-カルボン酸 t-ブチルエステル、ピラジン-2-カルボン酸、2'-フルオロビフェニル-4-オールを用いて、実施例 338 (工程 3) から (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 15 $^1\text{H NMR}$ (CDCl_3) δ : 1.20-2.50 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.80 (10H, m), 8.50-8.90 (2H, m), 9.40-10.00 (1H, m), 10.50-11.20 (1H, m)
ESI-MS (m/e) : 494 [M+H]

実施例 527

- 20 6-(1-アセチルピロリジン-2-イル)-5-((5-クロロピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

5-クロロ-3-ピリジノールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 25 $^1\text{H NMR}$ (CD_3OD) δ : 1.89 and 2.15 (total 3H, each s), 1.94-2.20 (3H, m), 2.29-2.49 (1H, m), 3.62-3.97 (2H, m), 5.32-5.40 (1H, m), 7.17-7.63 (4H, m), 7.94-8.04 (1H, m), 8.26-8.41 (3H, m), 8.73-8.79 (1H, m)

ESI-MS (m/e) : 434 [M+H]

実施例 528

1- (5- ((6- (1-アセチルピロリジン-2-イル) -2-ピリジン-
5 2-イル-1H-ベンズイミダゾール-5-イル) オキシ) ピリジン-2-イ
ル) ピロリジン-2-オン

1- (5-ヒドロキシピリジン-2-イル) ピロリジン-2-オンを用いて、
実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法と
を組み合わせることにより、表題化合物を油状物質として得た。

10 ¹HNMR (CDCl₃) δ : 1.79-2.43 (9H, m), 2.58-2.
71 (2H, m), 3.53-3.89 (2H, m), 3.98-4.17
(2H, m), 5.21-5.57 (1H, m), 6.77-7.57 (4H,
m), 7.74-8.66 (5H, m)

ESI-MS (m/e) : 483 [M+H]

15

実施例 529

6- (1-アセチルピロリジン-2-イル) -5- ((6-メチルピリジン-
3-イル) オキシ) -2-ピラジン-2-イル-1H-ベンズイミダゾール

6-メチルピリジン-3-オールを用いて、実施例 526 と同様の方法、こ
20 れに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を
白色固体として得た。

¹HNMR (CDCl₃) δ : 1.60-2.60 (10H, m), 3.50-
3.95 (2H, m), 5.20-5.60 (1H, m), 6.65-7.8
0 (4H, m), 8.20-8.40 (1H, m), 8.50-8.70 (2
25 H, m), 9.50-9.70 (1H, m), 10.60-11.40 (1H,
m)

ESI-MS (m/e) : 415 [M+H]

実施例 530

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - ([1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダゾール

6 - ([1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - オールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80 - 2.43 (7H, m), 3.57 - 3.92 (2H, m), 5.19 - 5.46 (1H, m), 6.98 - 8.43 (7H, m), 8.55 - 8.87 (3H, m), 10.53 - 10.74 (1H, m)

ESI-MS (m/e) : 468 [M+H]

実施例 531

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (1, 3 - オキサゾール - 4 - イル) フェノキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダゾール

4 - (1, 3 - オキサゾール - 4 - イル) フェノールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.89 - 2.20 (6H, m), 2.28 - 2.50 (1H, m), 3.62 - 4.00 (2H, m), 5.39 - 5.50 (1H, m), 7.12 - 7.53 (5H, m), 7.80 - 7.89 (2H, m), 7.93 - 8.04 (1H, m), 8.24 - 8.33 (3H, m), 8.70 - 8.79 (1H, m)

ESI-MS (m/e) : 466 [M+H]

実施例 532

6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - クロロピリジン - 3 - イル) オキシ) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール

6-クロロピリジン-3-オールを用いて、実施例526と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60–2.60 (7H, m), 3.50–3.95 (2H, m), 5.20–5.60 (1H, m), 6.65–8.30 (5H, m), 8.40–8.70 (2H, m), 9.50–9.70 (1H, m), 10.60–11.60 (1H, m)
ESI-MS (m/e): 435 [M+H]

10 実施例533

6-(1-アセチルピロリジン-2-イル)-5-(4-(2-メチル-2H-テトラゾール-5-イル)フェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

4-(2-メチル-2H-テトラゾール-5-イル)フェノールを用いて、実施例526と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.90–2.19 (6H, m), 2.27–2.51 (1H, m), 3.61–4.00 (2H, m), 4.43 and 4.44 (total 3H, each s), 5.38–5.46 (1H, m), 7.23 (2H, d, $J=8.6\text{ Hz}$), 7.24–7.60 (2H, m), 8.11–8.19 (2H, m), 8.67–8.70 (1H, m), 8.77 (1H, brs), 9.46 (1H, d, $J=8.6\text{ Hz}$)
ESI-MS (m/e): 482 [M+H]

25 実施例534

6-(1-アセチルピロリジン-2-イル)-5-(6-プロモピリジン-3-イル)オキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

6-プロモピリジン-3-オールを用いて、実施例526と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を

白色固体として得た。

^1H NMR (CDCl_3) δ : 1.60–2.50 (7H, m), 3.60–3.95 (2H, m), 5.20–5.50 (1H, m), 6.80–8.40 (5H, m), 8.50–8.80 (2H, m), 9.50–9.70 (1H, m), 10.40–11.10 (1H, m)
ESI-MS (m/e): 479, 481 [M+H]

実施例 535

5 – (1 – アセチル – 3 – フルオロピロリジン – 2 – イル) – 6 – (4 – (メ
10 タンスルホニル) フェノキシ) – 2 – ピリジン – 2 – イル – 1 H – ベンズイミダ
ゾール エナンチオマー A、及びエナンチオマー B

実施例 493 で得られた、5 – (1 – アセチル – 3 – フルオロピロリジン –
2 – イル) – 6 – (4 – (メタンスルホニル) フェノキシ) – 2 – ピリジン – 2
– イル – 1 H – ベンズイミダゾール ジアステレオマー B 10mg を 光学分割
15 用カラム (CHIRALPAK AD 2 cm ϕ \times 25 cm L (ダイセル化学
工業社製)、移動相: ヘキサン/エタノール/ジエチルアミン = 40/60/
0.1、流速: 10 ml/min) にて光学分割し、エナンチオマー A (保持時
間: 10.5 min)、及びエナンチオマー B (保持時間: 19.0 min) を
それぞれ白色固体として得た。

20 エナンチオマー A

ESI-MS (m/e): 495 [M+H]

エナンチオマー B

ESI-MS (m/e): 495 [M+H]

25 実施例 536

6 – (1 – アセチルピロリジン – 2 – イル) – 5 – ((6 – (1 – メチル – 1
H – テトラゾール – 5 – イル) ピリジン – 3 – イル) オキシ) – 2 – ピリジン
– 2 – イル – 1 H – ベンズイミダゾール

6 – (1 – メチル – 1 H – テトラゾール – 5 – イル) ピリジン – 3 – オール

を用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CD₃OD) δ: 1.88 and 2.02 (total 3H, each s), 1.93–2.20 (3H, m), 2.28–2.50 (1H, m), 3.60–4.00 (2H, m), 4.47 and 4.48 (total 3H, each s), 5.32–5.42 (1H, m), 7.22–7.70 (4H, m), 7.95–8.02 (1H, m), 8.25–8.32 (2H, m), 8.61–8.64 (1H, m), 8.73 (1H, brs)
ESI-MS (m/e): 482 [M+H]

10

実施例 537

6-(1-アセチルピロリジン-2-イル)-5-((6-(1-メチル-1H-テトラゾール-5-イル)ピリジン-3-イル)オキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

15 6-(1-メチル-1H-テトラゾール-5-イル)ピリジン-3-オールを用いて、実施例 526 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CD₃OD) δ: 1.91 and 2.16 (total 3H, each s), 2.00–2.20 (3H, m), 2.38–2.55 (1H, m), 3.63–4.01 (2H, m), 4.50 and 4.51 (total 3H, each s), 5.35–5.44 (1H, m), 7.33–7.60 (2H, m), 7.66–7.73 (1H, m), 8.27–8.34 (1H, m), 8.65–8.67 (1H, m), 8.71–8.73 (1H, m), 8.78–8.80 (1H, m), 9.48–9.50 (1H, m)

25 ESI-MS (m/e): 483 [M+H]

実施例 538

6-(1-アセチルピロリジン-2-イル)-5-((6-(2-メチル-2H-テトラゾール-5-イル)ピリジン-3-イル)オキシ)-2-ピリジン

6-(2-メチル-2H-テトラゾール-5-イル)ピリジン-3-オール

6-(2-メチル-2H-テトラゾール-5-イル)ピリジン-3-オールを用いて、実施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 5 $^1\text{H NMR}$ (CD_3OD) δ : 1.91-2.20 (6H, m), 2.33-2.52 (1H, m), 3.60-4.00 (2H, m), 4.48-4.90 (3H, m), 5.37-5.44 (1H, m), 7.22-7.68 (4H, m), 7.97-8.04 (1H, m), 8.19-8.23 (1H, m), 8.25-8.31 (1H, m), 8.55-8.59 (1H, m), 8.74 (1H, brs)
- 10 ESI-MS (m/e): 482 [M+H]

実施例539

- 15 6-(1-アセチルピロリジン-2-イル)-5-(4-(5-メチル-1H-テトラゾール-1-イル)フェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

4-(5-メチル-1H-テトラゾール-1-イル)フェノールを用いて、実施例526と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

- 20 $^1\text{H NMR}$ (CD_3OD) δ : 1.91 and 2.16 (total 3H, eachs), 1.96-2.20 (3H, m), 2.33-2.54 (1H, m), 2.63 and 2.64 (total 3H, eachs), 3.64-4.00 (2H, m), 5.38-5.43 (1H, m), 7.32-7.57 (4H, m), 7.61-7.68 (2H, m), 8.70-8.73 (1H, m), 8.78-8.80 (1H, m), 9.47-9.49 (1H, m)
- 25 ESI-MS (m/e): 482 [M+H]

実施例540

- 6-(1-アセチルピロリジン-2-イル)-5-(6-(1H-ピラゾ-

ル-1-イル) ピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1
H-ベンズイミダゾール

6- (1H-ピラゾール-1-イル) ピリジン-3-オールを用いて、実施
例338 (工程5) と同様の方法、これに準じた方法又はこれらと常法とを組
5 み合わせることににより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.67-2.48 (7H, m), 3.50-3.
92 (2H, m), 5.14-5.57 (1H, m), 6.41-6.50
(1H, m), 6.80-8.03 (7H, m), 8.17-8.67 (4H,
m), 11.00-11.11.27 (1H, m)

10 ESI-MS (m/e): 466 [$\text{M}+\text{H}$]

実施例541

6- (1-アセチルピロリジン-2-イル) -2-ピリジン-2-イル-5-
((6- (1H-[1, 2, 4]-トリアゾール-1-イル) ピリジン-3-
15 イル) オキシ) -1H-ベンズイミダゾール

6- (1H-[1, 2, 4]-トリアゾール-1-イル) ピリジン-3-
オールを用いて、実施例338 (工程5) と同様の方法、これに準じた方法又
はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得
た。

20 $^1\text{H NMR}$ (CDCl_3) δ : 1.62-2.45 (7H, m), 3.52-3.
90 (2H, m), 5.20-5.55 (1H, m), 6.79-8.68
(10H, m), 9.02-9.13 (1H, m), 11.17-11.52
(1H, m)

ESI-MS (m/e): 467 [$\text{M}+\text{H}$]

25

実施例542

5- (4- (2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2
-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾー
ル エナンチオマーA及びエナンチオマーB

- 4- (2-メチル-2H-テトラゾール-5-イル) フェノールを用いて、
 実施例162 (工程2) ~ (工程7) と同様な方法で得られた5- (4- (2-
 メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-
 イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール59.0mg
 5 を、光学分割用カラム (CHIRALPAK AD 2cmφ×25cmL (ダイセル化学工業社製)、移動相: エタノール/2-プロパノール/ジエチル
 アミン 25/75/0.1、流速: 12~18ml/min) にて光学分割
 し、エナンチオマーA及びエナンチオマーBをそれぞれ淡黄色固体として得た。
 (保持時間: エナンチオマーA 13.5min, エナンチオマーB 30.
 10 8min, CHIRALPAK AD 4.6mmφ×250mmL (ダイセル化学工業社製)、移動相: エタノール/2-プロパノール/ジエチルアミン
 25/75/0.1、流速: 1ml/min)

実施例543

- 15 6- (1-アセチルピロリジン-2-イル) -5- (4- (2-メチル-2H-
 テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-
 ベンズイミダゾール エナンチオマーA

- 実施例542で得られた5- (4- (2-メチル-2H-テトラゾール-5-
 イル) フェノキシ) -2-ピリジン-2-イル-6-ピロリジン-2-イル
 20 -1H-ベンズイミダゾール エナンチオマーA 24.7mgのクロロホルム
 1ml溶液に、無水酢酸0.006mlを加え、反応液を室温で10分間攪拌
 した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー
 (Kieselgel TM60F254, Art 5744 (メルク社製)、ク
 ロロホルム/メタノール=10/1) にて精製し、表題化合物のキラル体の1
 25 つを白色固体として得た。

¹H NMR (CD₃OD) δ: 1.90-2.20 (6H, m), 2.24-2.49 (1H, m), 3.66-4.00 (2H, m), 5.37-5.46 (1H, m), 7.12-7.60 (5H, m), 7.94-8.04 (1H, m), 8.04-8.20 (2H, m), 8.29 (1H, t, J=8.2 Hz)

z), 8.68–8.78 (1H, m)

ESI-MS (m/e) : 481 [M+H]

実施例 544

5 6-(1-アセチルピロリジン-2-イル)-5-(4-(2-メチル-2H-テトラゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール エナンチオマーB

実施例 542 で得られた 5-(4-(2-メチル-2H-テトラゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール エナンチオマーB 30.9mg のクロロホルム 1ml 溶液に、無水酢酸 0.007ml を加えた後、反応液を室温で 10 分間
10 攪拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー (Kieselgel TM 60 F254, Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物のキラル体の
15 1つを白色固体として得た。

ESI-MS (m/e) : 481 [M+H]

実施例 545

20 5-(1-アセチル-5-メチルピロリジン-2-イル)-6-(4-(メタンスルホニル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール エナンチオマーA、B、C及びD

5-メチルジヒドロフラン-2(3H)-オンを用いて、実施例 485 と同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物の 4 成分混合物を得た。得られた 4 成分混合物 15mg を光学分割
25 用カラム (CHIRAL-CEL OD-H 2cmφ×25cmL (ダイセル化学工業社製)、移動相:ヘキサン/エタノール/ジエチルアミン=80/20/0.1) にて光学分割し、エナンチオマーA (保持時間:13.67min)、エナンチオマーB (保持時間:15.24min)、エナンチオマーC (保持時間:18.96min)、及びエナンチオマーD (保持時間:22.

90 min) をそれぞれ淡黄色固体として得た。

エナンチオマーA

$^1\text{H NMR}$ (CDCl_3) δ : 1.23–1.38 (3H, m), 1.50–2.57 (7H, m), 3.04 and 3.08 (3H, s), 4.24–4.60 (1H, m), 5.18–5.43 (1H, m), 6.92–7.83 (5H, m), 7.83–7.98 (3H, m), 8.34–8.43 (1H, m), 8.60–8.67 (1H, m), 10.84–11.33 (1H, m)

ESI-MS (m/e): 491 [M+H]

10 エナンチオマーB

$^1\text{H NMR}$ (CDCl_3) δ : 1.22–2.20 (9H, m), 2.23–2.45 (1H, m), 3.04 and 3.08 (3H, s), 4.10–4.22 (1H, m), 5.09–5.23 (1H, m), 7.04–7.70 (5H, m), 7.83–7.97 (3H, m), 8.34–8.48 (1H, m), 8.61–8.69 (1H, m), 10.73–11.16 (1H, m)

ESI-MS (m/e): 491 [M+H]

エナンチオマーC

ESI-MS (m/e): 491 [M+H]

20 エナンチオマーD

ESI-MS (m/e): 491 [M+H]

実施例546

6-(1-アセチルピロリジン-2-イル)-5-((6-(2-メチル-2H-テトラゾール-5-イル)ピリジン-3-イル)オキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

6-(2-メチル-2H-テトラゾール-5-イル)ピリジン-3-オールを用いて、実施例526と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

^1H NMR (CD_3OD) δ : 1.88–2.20 (6H, m), 2.21–2.31 (1H, m), 3.61–4.00 (2H, m), 4.46 and 4.47 (total 3H, each s), 5.34–5.44 (1H, m), 7.22–7.71 (3H, m), 8.18–8.25 (1H, m), 8.50–8.60 (1H, m), 8.65–8.70 (1H, m), 8.72–8.80 (1H, m), 9.44–9.47 (1H, m)
 ESI-MS (m/e): 483 [M+H]

実施例 547

10 6-(1-アセチルピロリジン-2-イル)-5-(4-(2-(メトキシメチル)-2H-テトラゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-(2-(メトキシメチル)-2H-テトラゾール-5-イル)フェノールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

15 ^1H NMR (CD_3OD) δ : 1.90–2.20 (6H, m), 2.22–2.71 (1H, m), 3.53 (3H, s), 5.38–5.46 (1H, m), 5.96 and 5.97 (total 3H, each s), 7.20–7.56 (5H, m), 7.95–8.03 (1H, m), 8.17–8.22 (2
 20 H, m), 8.29 (1H, t, $J=8.0\text{ Hz}$), 8.73–8.79 (1H, m)

ESI-MS (m/e): 511 [M+H]

実施例 548

25 6-(1-アセチルピロリジン-2-イル)-5-(6-(メトキシメチル)ピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

6-(メトキシメチル)ピリジン-3-オールを用いて、実施例 483 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、

表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60–2.43 (7H, m), 3.34–3.91 (5H, m), 4.45–4.59 (2H, m), 5.20–5.52 (1H, m), 6.86–7.67 (5H, m), 7.80–7.90 (1H, m), 8.29–8.48 (2H, m), 8.55–8.67 (1H, m), 10.87–11.27 (1H, m)
 ESI-MS (m/e): 444 [M+H]

実施例 549

10 2-(2-(5-(4-(2-メチル-2H-テトラゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-1-イル)-2-オキソエタノール

4-(2-メチル-2H-テトラゾール-5-イル)フェノールを用いて、実施例 162 (工程 2) ~ (工程 7) と同様な方法で得られた 5-(4-(2-メチル-2H-テトラゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾールを用いて、実施例 168 と同様な方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.94–2.16 (3H, m), 2.23–2.48 (1H, m), 3.57–4.34 (4H, m), 4.43 and 4.44 (total 3H, each s), 5.27–5.52 (1H, m), 7.17–7.57 (5H, m), 7.94–8.04 (1H, m), 8.09–8.20 (2H, m), 8.24–8.32 (1H, m), 8.69–8.81 (1H, m)
 25 ESI-MS (m/e): 497 [M+H]

実施例 550

6-(1-アセチル-3-フルオロピロリジン-2-イル)-5-(6-(5-メチル-[1,2,4]-オキサジアゾール-3-イル)ピリジン-

3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

実施例493で得られたN-(4-(1-アセチル-3-フルオロピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキシアミド ジアステレオマーB、及び6-(5-メチル-[1,2,4]-オキサジアゾール-3-イル)ピリジン-3-オールを用いて、実施例338 (工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をとして得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.82-2.43 (5H, m), 2.68 and 2.70 (3H, s), 3.64-4.40 (2H, m), 5.19-5.40 (1H, m), 5.42-5.64 (1H, m), 7.02-7.79 (4H, m), 7.80-7.92 (1H, m), 8.00-8.12 (1H, m), 8.35-8.42 (1H, m), 8.60-8.75 (2H, m), 10.50-10.68 (1H, m)

ESI-MS (m/e): 500 $[\text{M}+\text{H}]$

15

実施例551

6-(1-アセチルピロリジン-2-イル)-5-(4-(2-エチル-2H-テトラゾール-5-イル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

20 4-(2-エチル-2H-テトラゾール-5-イル)フェノールを用いて、実施例338 (工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.68 (3H, t, $J=7.2\text{ Hz}$), 1.90 and 2.13 (total 3H, each s), 1.97-2.20 (3H, m), 2.29-2.53 (1H, m), 3.62-4.00 (2H, m), 4.73-7.79 (2H, m), 5.37-5.47 (1H, m), 7.19-7.60 (5H, m), 7.93-8.03 (1H, m), 8.10-8.20 (2H, m), 8.23-8.33 (1H, m), 8.74 (1H, brs)

E S I - M S (m/e) : 495 [M+H]

実施例 552

2 - (5 - (4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノキシ
5) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 6 - イル) ピロリ
ジン - 1 - カルボキサミド

4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノールを用いて、
実施例 162 (工程 2) ~ (工程 7) と同様な方法で得られた 5 - (4 - (2
- メチル - 2 H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピリジン - 2
10 - イル - 6 - ピロリジン - 2 - イル - 1 H - ベンズイミダゾールを用いて、実
施例 184 と同様な方法、これに準じた方法又はこれらと常法とを組み合わせ
ることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.97 - 2.10 (3H, m), 2.28 - 2.
41 (1H, m), 3.52 - 3.63 (1H, m), 3.74 - 3.62 (
15 1H, m), 5.26 - 5.41 (1H, m), 7.10 - 7.33 (1H,
m), 7.23 (2H, d, $J = 8.8\text{ Hz}$), 7.44 - 7.61 (2H,
m), 7.95 - 7.99 (1H, m), 8.12 (2H, d, $J = 8.8\text{ Hz}$),
8.27 (1H, d, $J = 8.2\text{ Hz}$), 8.72 - 8.73 (1H,
m)

20 E S I - M S (m/e) : 482 [M+H]

実施例 553

6 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 5 - (4 - (2
- メチル - 2 H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピリジン - 2
25 - イル - 1 H - ベンズイミダゾール

4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノールを用いて、
実施例 550 と同様な方法、これに準じた方法又はこれらと常法とを組み合わ
せることにより、表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CD_3OD) δ : 1.83 - 2.17 (total 3H, each

s), 2.10–2.40 (2H, m), 3.62–4.21 (2H, m),
 4.41 and 4.42 (total 3H, each s), 5.23–5.4
 3 (1H, m), 5.46–5.73 (1H, m), 7.10–7.65 (5
 H, m), 7.94–8.02 (1H, m), 8.03–8.17 (2H, m
 5) , 8.27 (1H, t, J=8.8 Hz), 8.72 (1H, brs)
 ESI-MS (m/e) : 499 [M+H]

実施例 554

5'-((2-ピリジン-2-イル-6-ピロリジン-2-イル-1H-ベン
 10 ズイミダゾール-5-イル) オキシ) -2H-1, 2'-ビピリジン-2-オ
ン エナンチオマーA及びエナンチオマーB

5'-ヒドロキシ-2H-1, 2'-ビピリジン-2-オンを用いて、実施
 例162 (工程2) ~ (工程7) と同様な方法で得られた5'-((2-ピリ
 ジン-2-イル-6-ピロリジン-2-イル-1H-ベンズイミダゾール-5
 15 -イル) オキシ) -2H-1, 2'-ビピリジン-2-オン15.0mgを光
 学分割用カラム (CHIRALPAK AD 2cmφ×25cmL (ダイセ
 ル化学工業社製)、移動相: 2-プロパノール、流速: 10ml/min) に
 て光学分割し、エナンチオマーA (保持時間: 23.6min)、エナンチオ
 マーB (保持時間: 50.7min) をそれぞれ淡黄色固体として得た。

20

実施例 555

5'-((6-(1-アセチルピロリジン-2-イル) -2-ピリジン-2-
イル-1H-ベンズイミダゾール-5-イル) オキシ) -2H-1, 2'-ビ
 25 ピリジン-2-オン エナンチオマーA

実施例554で得られた5'-((2-ピリジン-2-イル-6-ピロリジ
 ン-2-イル-1H-ベンズイミダゾール-5-イル) オキシ) -2H-1,
 2'-ビピリジン-2-オン エナンチオマーA 6.5mgのクロロホルム1
 ml溶液に、無水酢酸0.003mlを加えた後、反応液を室温で30分間攪
 拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィ

ー (Kieselgel TM60F254, Art 5744 (メルク社製)、
クロロホルム/メタノール=10/1) にて精製し、表題化合物のキラル体の
1つを白色固体として得た。

¹HNMR (CD₃OD) δ: 1.91 and 2.16 (total 3H,
5 each s), 1.94–2.20 (3H, m), 2.32–2.52 (1
H, m), 3.63–3.98 (2H, m), 5.38–5.44 (1H, m
) , 6.49–6.54 (1H, m), 6.63–6.68 (1H, m), 7.
23–7.58 (3H, m), 7.60–7.67 (2H, m), 7.77 (
1H, dd, J=8.8, 15.8 Hz), 7.87–7.93 (1H, m),
10 7.95–8.01 (1H, m), 8.27–8.31 (1H, m), 8.4
1 (1H, d, J=2.9 Hz), 8.73 (1H, t, J=4.7 Hz)
ESI-MS (m/e): 493 [M+H]

実施例 556

15 5' – ((6 – (1 – アセチルピロリジン – 2 – イル) – 2 – ピリジン – 2 –
イル – 1H – ベンズイミダゾール – 5 – イル) オキシ) – 2H – 1, 2' – ビ
ピリジン – 2 – オン エナンチオマー B

実施例 554 で得られた 5' – ((2 – ピリジン – 2 – イル – 6 – ピロリジ
ン – 2 – イル – 1H – ベンズイミダゾール – 5 – イル) オキシ) – 2H – 1,
20 2' – ビピリジン – 2 – オン エナンチオマー B 5.8 mg のクロロホルム 1
ml 溶液に、無水酢酸 0.003 ml を加えた後、反応液を室温で 30 分間攪
拌した。反応溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー
ー (Kieselgel TM60F254, Art 5744 (メルク社製)、
クロロホルム/メタノール=10/1) にて精製し、表題化合物のキラル体の
25 1つを白色固体として得た。

ESI-MS (m/e): 493 [M+H]

実施例 557

6 – (シス – 1 – アセチル – 4 – フルオロピロリジン – 2 – イル) – 5 – (4

－（２－メチル－２Ｈ－テトラゾール－５－イル）フェノキシ）－２－ピリジ
ン－２－イル－１Ｈ－ベンズイミダゾール

実施例 3 2 5（工程 5）で得られたシス－１－アセチル－２－（５－ニトロ
 5 ）－４－フルオロ－４－（（ピリジン－２－カルボニル）－アミノ）－フェニル
 ５－イル）フェノールを用いて、実施例 3 2 5（工程 6）と同様の方法、これ
 に準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白
 色固体として得た。

¹H NMR (CD₃OD) δ : 1. 8 0－2. 8 4 (2H, m), 1. 9 4 a
 10 n d 2. 2 5 (t o t a l 3 H, e a c h s), 3. 9 0－4. 3 0 (2
 H, m), 4. 4 3 (3H, s), 5. 2 8－5. 5 0 (1H, m), 5. 5
 1－5. 5 9 (1H, m), 7. 1 8－7. 6 4 (5H, m), 7. 9 4－8.
 0 1 (1H, m), 8. 1 2－8. 1 8 (2H, m), 8. 2 5－8. 2 9 (
 1H, m), 8. 7 0－8. 7 7 (1H, m)
 15 E S I－M S (m/e) : 4 9 9 [M+H]

実施例 5 5 8

3－（４－（（６－（１－アセチルピロリジン－２－イル）－２－ピリジン－
２－イル－１Ｈ－ベンズイミダゾール－５－イル）オキシ）フェニル）－１，
 20 ３－オキサゾリジン－２－オン

３－（４－ヒドロキシフェニル）－１，３－オキサゾリジン－２－オンを用
 いて、実施例 4 8 3と同様の方法、これに準じた方法又はこれらと常法とを組
 み合わせることににより、表題化合物を黄色油状物質として得た。

¹H NMR (CDCl₃) δ : 1. 2 0－2. 5 0 (7H, m), 3. 5 0－4.
 25 0 0 (2H, m), 3. 9 0－4. 2 5 (2H, m), 4. 4 0－4. 6 0
 (2H, m), 5. 2 0－5. 6 0 (1H, m), 6. 8 0－7. 7 0 (7H,
 m), 7. 8 0－8. 0 0 (1H, m), 8. 2 5－8. 5 0 (1H, m),
 8. 5 0－8. 8 0 (1H, m), 10. 5 0－10. 8 0 (1H, m)
 E S I－M S (m/e) : 4 8 4 [M+H]

実施例 559

6-(1-アセチルピロリジン-2-イル)-5-((6-メチルピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 5 6-メチルピリジン-3-オールを用いて、実施例 483 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.72-2.59 (10H, m), 3.53-3.90 (2H, m), 5.20-5.55 (1H, m), 6.81-7.66 (5H, m), 7.78-7.92 (1H, m), 8.28-8.43 (2H, m), 8.55-8.66 (1H, m), 11.07-11.55 (1H, m)

ESI-MS (m/e): 414 [M+H]

15 実施例 560

6-(1-アセチルピロリジン-2-イル)-5-((6-ピラジン-2-イルピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

- 20 6-ピラジン-2-イルピリジン-3-オールを用いて、実施例 483 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 0.80-2.40 (7H, m), 3.60-3.90 (2H, m), 5.20-5.60 (1H, m), 7.00-7.80 (4H, m), 7.80-8.00 (1H, m), 8.30-8.50 (2H, m), 8.50-8.80 (4H, m), 9.50-9.70 (1H, m), 10.40-10.80 (1H, m)

ESI-MS (m/e): 478 [M+H]

実施例 561

6-(シス-1-アセチル-4-フルオロピロリジン-2-イル)-5-
((2'-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イ
ル-1H-ベンズイミダゾール

実施例325(工程5)で得られたシス-1-アセチル-2-(5-ニトロ
 5 -2-フルオロ-4-((ピリジン-2-カルボニル)-アミノ)-フェニル
)-4-アセトキシ-ピロリジン、及び2'-フルオロビフェニル-4-オー
 ルを用いて、実施例325(工程6)と同様の方法、これに準じた方法又はこ
 れらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得
 た。

- 10 $^1\text{H NMR}$ (CDCl_3) δ : 0.80-2.80 (6H, m), 3.80-4.
 40 (2H, m), 5.05-5.50 (1H, m), 7.00-7.70
 (11H, m), 7.75-7.95 (1H, m), 8.30-8.50 (1
 H, m), 8.50-8.75 (1H, m), 10.60-10.80 (1H,
 m)
 15 ESI-MS (m/e): 511 [M+H]

実施例562

- 6-(シス-1-アセチル-4-フルオロピロリジン-2-イル)-5-
(4-ピラジン-2-イルフェノキシ)-2-ピリジン-2-イル-1H-ベ
 20 ンズイミダゾール

実施例325(工程5)で得られたシス-1-アセチル-2-(5-ニトロ
 -2-フルオロ-4-((ピリジン-2-カルボニル)-アミノ)-フェニル
)-4-アセトキシ-ピロリジン、及び4-ピラジン-2-イルフェノールを
 用いて、実施例325(工程6)と同様の方法、これに準じた方法又はこれら
 25 と常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

- $^1\text{H NMR}$ (CDCl_3) δ : 1.20-2.80 (6H, m), 3.80-4.
 40 (2H, m), 5.20-5.50 (1H, m), 7.00-7.70
 (5H, m), 7.80-7.95 (1H, m), 7.95-8.20 (2H,

m), 8.30-8.50 (2H, m), 8.50-8.80 (2H, m),
 8.95-9.20 (1H, m), 10.60-10.80 (1H, m)
 ESI-MS (m/e) : 495 [M+H]

5 実施例 563

N-((5-((6-(1-アセチルピロリジン-2-イル)-2-ピリジ
 ン-2-イル-1H-ベンズイミダゾール-5-イル) オキシ) ピリジン-
 2-イル) メチル) アセタミド

- 10 N-((5-ヒドロキシピリジン-2-イル) メチル) アセタミドを用いて、
 実施例 483 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

¹HNMR (CDCl₃) δ : 1.83-2.47 (10H, m), 3.54-
 3.90 (2H, m), 4.48-4.59 (2H, m), 5.21-5.5
 0 (1H, m), 6.66-7.69 (6H, m), 7.79-7.91 (1
 15 H, m), 8.30-8.44 (2H, m), 8.54-8.69 (1H,
 m), 10.96-11.29 (1H, m)
 ESI-MS (m/e) : 471 [M+H]

実施例 564

- 20 6-(1-アセチルピロリジン-2-イル)-5-((6-フルオロピリジ
 ン-3-イル) オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾー
 ル

- 6-フルオロピリジン-3-オールを用いて、実施例 338 (工程 5) と同
 様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
 25 表題化合物を黄色油状物質として得た。

¹HNMR (CDCl₃) δ : 1.40-2.50 (7H, m), 3.50-4.
 00 (2H, m), 5.00-5.60 (1H, m), 6.80-7.70
 (5H, m), 7.80-7.95 (1H, m), 8.00-8.15 (1H,

m), 8.25-8.50 (1H, m), 8.50-8.70 (1H, m),
 10.60-10.80 (1H, m)
 ESI-MS (m/e) : 418 [M+H]

5 実施例 565

シス-1-(4-フルオロ-2-(6-(6-シアノーピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマーA及びエナンチオマーB
 (工程1)

- 10 シス-1-(4-フルオロ-2-(6-(6-シアノーピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンの合成

実施例 325 (工程5) で得られたシス-1-アセチル-2-(5-ニトロ-2-フルオロ-4-(ピリジン-2-カルボニル)-アミノ)-フェニル)-4-アセトキシ-ピロリジン、及び6-シアノーピリジン-3-オールを用いて、実施例 325 (工程6) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

(工程2)

- 20 シス-1-(4-フルオロ-2-(6-(6-シアノーピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン エナンチオマーA及びエナンチオマーBの製造

(工程1) で得られたラセミ体のシス-1-(4-フルオロ-2-(6-(6-シアノーピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノンを
 25 用いて、実施例 333 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物をそれぞれ得た。

エナンチオマーA

^1H NMR (CD_3OD) δ : 1.91 (3H x 1/2, s), 2.22 (3H x 1/2, s), 2.32–2.67 (2H, m), 3.95–4.30 (2H, m), 5.27–5.47 (2H, m), 7.35–7.64 (3H, m), 7.85–7.92 (1H, m), 7.97–7.99 (1H, m),
 5 8.29 (1H, t, $J=7.6\text{Hz}$), 8.60 (1H, d, $J=3.1\text{Hz}$), 8.74 (1H, s).

ESI-MS (m/e): 443 [$M+H$]

エナンチオマーB

ESI-MS (m/e): 443 [$M+H$]

10

実施例566

6-(1-アセチル-3-フルオロピロリジン-2-イル)-5-(2-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1 H-ベンズイミダゾール エナンチオマーA

15 (工程1)

N-(4-(1-アセチル-3-フルオロピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド エナンチオマーA、及びエナンチオマーBの合成

実施例493で得られたN-(4-(1-アセチル-3-フルオロピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド ジアステレオマーB 300mgを光学分割用カラム(CHIRAL
 20 CEL OD 2cm ϕ ×25cmL(ダイセル化学工業社製)、移動相:ヘキサン/エタノール/ジエチルアミン=50/50/0.1、流速:10ml/min)にて光学分割し、エナンチオマーA、及びエナンチオマーをそれぞれ
 25 黄色固体として得た。

(工程2)

6-(1-アセチル-3-フルオロピロリジン-2-イル)-5-(2-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1 H-ベンズイミダゾール エナンチオマーAの製造

N- (4- (1-アセチル-3-フルオロピロリジン-2-イル) -5-フル
 ルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド エナンチオ
 マーA、及び2'-フルオロビフェニル-4-オールを用いて、実施例338
 (工程5)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ
 ることにより、表題化合物を得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.82-2.43 (5H, m), 3.63-4.
 36 (2H, m), 5.25-5.70 (2H, m), 7.07-7.58
 (11H, m), 7.74-7.90 (1H, m), 8.35-8.43 (1
 H, m), 8.58-8.68 (1H, m), 10.37-10.60 (1H,
 m)

ESI-MS (m/e): 511 $[\text{M}+\text{H}]$

実施例567

6- (1-アセチル-3-フルオロピロリジン-2-イル) -5- ((2'-
フルオロビフェニル-4-イル) オキシ)-2-ピリジン-2-イル-1 H-ベ
ンズイミダゾール エナンチオマーB

実施例566 (工程1) で得られたN- (4- (1-アセチル-3-フルオ
 ロピロリジン-2-イル) -5-フルオロ-2-ニトロフェニル)ピリジン-
 2-カルボキサミド エナンチオマーBを用いて、実施例566 (工程2)と同
 様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、
 表題化合物を得た。

ESI-MS (m/e): 511 $[\text{M}+\text{H}]$

実施例568

シス-1- (4-フルオロ-2- (6- (4-エタンスルホニル-フェノキ
シ)-2-ピリジン-2-イル-3 H-ベンズイミダゾール-5-イル) -ピ
ロリジン-1-イル) -エタノン

4-エタンスルホニルフェノールを用いて、実施例565（工程1）と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

^1H NMR (CD_3OD) δ : 1.90 (3H x 0.5, s), 2.22 (3H x 0.5, s), 2.25-2.75 (2H, m), 3.88-4.39 (2H, m), 5.24-5.48 (2H, m), 7.23-7.75 (5H, m), 7.90-8.02 (3H, m), 8.27-8.30 (1H, m), 8.73-8.75 (1H, m).

ESI-MS (m/e): 509 [M+H]

10

実施例569

3-(4-(6-(1-アセチルピロリジン-2-イル)-2-ピラジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)フェニル)-1,3-オキサゾリジン-2-オン エナンチオマーA

15 (工程1)

t-ブチル 2-(2-フルオロ-4-(ピラジン-2-イルカルボニル)アミノ)フェニル)ピロリジン-1-カルボキシレートの合成

実施例338（工程2）で得られた2-(4-アミノ-2-フルオロフェニル)-ピロリジン-1-カルボン酸 t-ブチルエステル3gのピリジン50ml溶液に、ピラジン-2-カルボン酸1.5g、1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・一塩酸塩3.1gを順次加え、反応液を室温にて3時間攪拌した。反応液を、クロロホルムにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム/メタノール=50/1）にて精製し、表題化合物を黄色油状物質として得た。

20

25

(工程2)

N-(3-フルオロ-4-ピロリジン-2-イルフェニル)ピラジン-2-カルボキサミド二塩酸塩の合成

5 t-ブチル 2-(2-フルオロ-4-(ピラジン-2-イルカルボニル)アミノ)フェニル)ピロリジン-1-カルボキシレート 4.4 g のメタノール 50 ml 溶液に、4 規定塩酸-ジオキサン溶液 50 ml を加え、反応液を室温にて 1 時間攪拌した。溶媒を減圧留去し表題化合物を黄色固体として得た。

(工程 3)

N-(4-(1-アセチルピロリジン-2-イル)-3-フルオロフェニル)ピラジン-2-カルボキサミドの合成

10 N-(3-フルオロ-4-ピロリジン-2-イルフェニル)ピラジン-2-カルボキサミド二塩酸塩 4.3 g のピリジン 50 ml 溶液に、無水酢酸 1.5 ml を加え、反応液を室温にて 20 分間攪拌した。反応液をクロロホルムにて希釈し、水、飽和食塩水にて順次洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム/メタノール=50/1）にて精製し、表題化合物を黄色固体として得た。

(工程 4)

N-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピラジン-2-カルボキサミドの合成

20 N-(4-(1-アセチルピロリジン-2-イル)-3-フルオロフェニル)ピラジン-2-カルボキサミド 3.9 g に、氷冷下、発煙硝酸 40 ml 加え、反応液を室温にて 2 時間攪拌した。反応液を氷水で希釈し飽和重曹水で塩基性とした後、クロロホルムにて抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：クロロホルム/メタノール=50/1）にて精製し、表題化合物を黄色油状物質として得た。

(工程 5)

25 N-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピラジン-2-カルボキサミド エナンチオマー A 及びエナンチオマー B の合成

N-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニ
トロフェニル)ピラジン-2-カルボキサミド 50.0mg を光学分割用カラム
(CHIRALPAK OD-H 2cmφ×25cmL (ダイセル化学工業
社製)、移動相:ヘキサン/2-プロパノール 1/1、流速:15ml/min)
5 n)にて光学分割し、エナンチオマーA(保持時間:18min)、エナンチ
オマーB(保持時間:25min)をそれぞれ淡黄色油状物質として得た。

(工程6)

3-(4-(6-(1-アセチルピロリジン-2-イル)-2-ピラジン-
2-イル-1H-ベンズイミダゾール-5-イル)オキシ)フェニル)-1,
10 3-オキサゾリジン-2-オン エナンチオマーAの製造

3-(4-ヒドロキシフェニル)-1, 3-オキサゾリジン-2-オン及び
N-(4-(1-アセチルピロリジン-2-イル)-5-フルオロ-2-ニ
トロフェニル)ピラジン-2-カルボキサミド エナンチオマーAを用いて、実
施例338(工程5)と同様の方法、これに準じた方法又はこれらと常法とを
15 組み合わせることにより、表題化合物のキラル体の1つを黄色油状物質として
得た。

¹HNMR (CDCl₃) δ: 1.00-2.40 (7H, m), 3.50-3.
90 (2H, m), 3.90-4.20 (2H, m), 4.40-4.60
(2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (6H,
20 m), 8.50-8.75 (2H, m), 9.50-9.70 (1H, m),
10.30-10.60 (1H, m)

ESI-MS (m/e): 485 [M+H]

実施例570

25 3-(4-(6-(1-アセチルピロリジン-2-イル)-2-ピラジン-
2-イル-1H-ベンズイミダゾール-5-イル)オキシ)フェニル)-1,
3-オキサゾリジン-2-オン エナンチオマーB

3-(4-ヒドロキシフェニル)-1, 3-オキサゾリジン-2-オン及び
実施例569(工程5)で得られたN-(4-(1-アセチルピロリジン-

2-イル) - 5-フルオロ-2-ニトロフェニル) ピラジン-2-カルボキサミド エナンチオマーBを用いて、実施例338 (工程5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

5 ESI-MS (m/e) : 485 [M+H]

実施例571

6-(1-アセチルピロリジン-2-イル)-5-(4-(シクロプロピルスルホニル) フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

10 ル

4-(シクロプロピルスルホニル) フェノールを用いて、実施例483と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を微黄色固体として得た。

¹HNMR (CDCl₃) δ : 0.90-1.20 (2H, m), 1.20-1.40 (3H, m), 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.50 (1H, m), 7.00-8.20 (8H, m), 8.30-8.50 (1H, m), 8.55-8.80 (1H, m), 10.70-11.20 (1H, m)

15 ESI-MS (m/e) : 503 [M+H]

20

実施例572

6-(1-アセチルピロリジン-2-イル)-5-(4-(エタンスルホニル) フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4-(エタンスルホニル) フェノールを用いて、実施例483と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹HNMR (CDCl₃) δ : 1.20-1.40 (3H, m), 1.60-2.50 (7H, m), 3.00-3.20 (2H, m), 3.50-4.00 (2H, m), 5.10-5.50 (1H, m), 6.90-7.80 (5H,

m), 7.80–8.00 (3H, m), 8.30–8.50 (1H, m),
 8.50–8.75 (1H, m), 10.60–11.20 (1H, m)
 ESI-MS (m/e) : 491 [M+H]

5 実施例 573

シス-1-(4-フルオロ-2-(6-(6-エタンスルホニル-ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

6-エタンスルホニル-ピリジン-3-オールを用いて、実施例 565 (工程 1) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CD₃OD) δ : 1.20–1.40 (3H, m), 1.90–2.30 (3H, m), 2.00–2.80 (2H, m), 3.20–3.50 (2H, m), 3.84–4.25 (2H, m), 5.27–5.45 (2H, m), 7.40–7.80 (4H, m), 8.00–8.20 (2H, m), 8.24–8.40 (1H, m), 8.66 (1H, s), 8.80 (1H, br s)
 ESI-MS (m/e) : 510 [M+H]

20 実施例 574

シス-1-(4-フルオロ-2-(6-(6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-イルオキシ)-2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル)-ピロリジン-1-イル)-エタノン

6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-オールを用いて、実施例 565 (工程 1) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

¹HNMR (CD₃OD) δ : 1.90–2.30 (3H, m), 2.00–2.80 (2H, m), 2.75 (3H, s), 3.84–4.40 (2H, m),

5. 30-5. 45 (2H, m), 7. 25-7. 80 (4H, m), 7. 90-8. 40 (3H, m), 8. 55-8. 68 (1H, m), 8. 75 (1H, s)

ESI-MS (m/e) : 500 [M+H]

5

実施例 575

5-(6-(1-アセチル-3-フルオロピロリジン-2-イル)-2-ピロリジン-2-イル-1H-ベンズイミダゾール-5-イル) オキシ) ピリジン-2-カルボニトリル

- 10 実施例 566 (工程 1) で得られた N-(4-(1-アセチル-3-フルオロピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキシアミド エナンチオマー B、及び 5-ヒドロキシピリジン-2-カルボニトリルを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1. 54-2. 45 (5H, m), 3. 61-4. 34 (2H, m), 5. 09-5. 54 (2H, m), 7. 01-7. 95 (6H, m), 8. 34-8. 47 (1H, m), 8. 54-8. 73 (2H, m), 10. 66-10. 79 (1H, m)

- 20 ESI-MS (m/e) : 443 [M+H]

実施例 576

- 6-(1-アセチル-3-フルオロピロリジン-2-イル)-5-(6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-イル) オキシ)-2-ピロリジン-2-イル-1H-ベンズイミダゾール

6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-オールを用いて、実施例 575 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1. 54-2. 45 (5H, m), 3. 61-4.

3.4 (2H, m), 5.09–5.54 (2H, m), 7.01–7.95
(6H, m), 8.34–8.47 (1H, m), 8.54–8.73 (2H,
m), 10.66–10.79 (1H, m)

ESI-MS (m/e) : 443 [M+H]

5

実施例 577

6-(1-アセチルピロリジン-2-イル)-2-ピラジン-2-イル-5-
((6-ピラジン-2-イルピリジン-3-イル) オキシ)-1H-ベンズイ
ミダゾール

- 10 6-ピラジン-2-イルピリジン-3-オールを用いて、実施例 570 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色油状物質として得た。

¹H NMR (CDCl₃) δ : 1.05–2.50 (7H, m), 3.50–4.00 (2H, m), 5.20–5.60 (1H, m), 7.00–7.80
15 (3H, m), 8.20–8.45 (1H, m), 8.45–8.80 (5H, m), 9.50–9.70 (2H, m), 10.40–11.30 (1H, m)

ESI-MS (m/e) : 479 [M+H]

20 実施例 578

6-(1-アセチル-5-メチルピロリジン-2-イル)-5-((6-メチ
ルピリジン-3-イル) オキシ)-2-ピリジン-2-イル-1H-ベンズイ
ミダゾール

- 25 実施例 545 で得られた、N-(4-(1-アセチル-5-メチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピリジン-2-カルボキサミド、及び 6-メチルピリジン-3-オールを用いて、実施例 338 (工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.20–2.30 (7H, m), 2.30–2.70 (6H, m), 4.05–4.60 (1H, m), 5.20–5.60 (1H, m), 6.80–7.50 (4H, m), 7.70–7.90 (1H, m), 8.15–8.20 (1H, m), 8.25–8.40 (2H, m), 8.50–8.80 (1H, m)
 ESI-MS (m/e): 428 [M+H]

実施例 579

6-(1-アセチル-5-メチルピロリジン-2-イル)-5-((6-クロロピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

6-クロロピリジン-3-オールを用いて、実施例 578 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.20–2.60 (10H, m), 4.05–4.65 (1H, m), 5.10–5.50 (1H, m), 6.80–7.70 (4H, m), 7.80–8.10 (2H, m), 8.15–8.50 (2H, m), 8.60–8.80 (1H, m), 10.80–11.30 (1H, m)
 ESI-MS (m/e): 448 [M+H]

実施例 580

2-(5-((6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-イルスルファニル)エタノール

実施例 504 で得られた 6-(1-アセチルピロリジン-2-イル)-5-((6-クロロピリジン-3-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール 20mg の N, N-ジメチルホルムアミド 1ml 溶液に、2-メルカプトエタノール 20mg、及び炭酸カリウム 10mg を順次加

え、反応液を120度にて5時間攪拌した。冷却後、反応液を飽和重曹水にて希釈し、クロロホルムにて抽出、有機層を無水硫酸マグネシウムにて乾燥し、溶媒を減圧留去した。得られた残渣を分取用薄層クロマトグラフィー (Kieselgel™ 60 F₂₅₄、Art 5744 (メルク社製)、クロロホルム/メタノール=10/1) にて精製し、表題化合物を白色固体として得た。

¹H NMR (CDCl₃) δ: 1.10–2.50 (7H, m), 3.20–3.40 (2H, m), 3.50–4.00 (4H, m), 5.20–5.50 (1H, m), 6.80–7.70 (5H, m), 7.80–7.95 (1H, m), 8.10–8.50 (2H, m), 8.50–8.70 (1H, m), 10.60–10.80 (1H, m)
ESI-MS (m/e): 476 [M+H]

実施例 581

3-(5-(6-(1-アセチルピロリジン-2-イル)-2-ピリジン-2-イル-1H-ベンズイミダゾール-5-イル)オキシ)ピリジン-2-イルスルファニル)プロパン-1-オール

3-メルカプトプロパン-1-オールを用いて、実施例 580 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹H NMR (CDCl₃) δ: 1.60–2.50 (7H, m), 3.20–3.40 (2H, m), 3.50–4.40 (6H, m), 5.20–5.60 (1H, m), 6.80–7.70 (5H, m), 7.80–7.95 (1H, m), 8.20–8.50 (2H, m), 8.50–8.70 (1H, m), 10.80–11.20 (1H, m)
ESI-MS (m/e): 490 [M+H]

実施例 582

6-(1-アセチルピロリジン-2-イル)-2-(5-メチルピリジン-2-イル)-5-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミ

ダゾール

5-メチルピコリン酸を用いて、実施例462と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- 5 ^1H NMR (CD_3OD) δ : 1.86 and 2.10 (total 3H, each s), 1.92-2.43 (4H, m), 2.65 and 2.66 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.62-3.96 (2H, m), 5.25-5.32 (1H, m), 7.23 and 7.25 (total 2H, each d, $J=8.8\text{Hz}$), 7.20-7.58 (3H, m), 7.95 and 7.99 (total 2H, each d, $J=8.8\text{Hz}$), 8.38-8.42 (1H, m), 9.12-9.16 (1H, m)
- 10 ESI-MS (m/e): 491 $[\text{M}+\text{H}]$

15 実施例583

6-(1-アセチルピロリジン-2-イル)-2-(5-メチルピラジン-2-イル)-5-(4-メタンスルホニル-フェノキシ)-1H-ベンズイミダゾール

- 5-メチルピラジン-2-カルボン酸を用いて、実施例462と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。
- 20

- ^1H NMR (CD_3OD) δ : 1.87-2.45 (7H, m), 2.66 and 2.67 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.63-4.00 (2H, m), 5.26-5.34 (1H, m), 7.20-7.61 (4H, m), 7.96 and 7.99 (total 2H, each d, $J=8.8\text{Hz}$), 8.69 (1H, s), 9.32 and 9.34 (total 1H, each s)
- 25 ESI-MS (m/e): 492 $[\text{M}+\text{H}]$

実施例 584

1 - (4 - ((6 - (1 - アセチル - 3 - フルオロピリジン - 2 - イル) -
2 - ピリジン - 2 - イル - 1H - ベンズイミダゾール - 5 - イル) オキシ)

5 フェニル) エタノン

1 - (4 - ヒドロキシフェニル) エタノンを用いて、実施例 575 と同様の
方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
化合物を油状物質として得た。

¹H NMR (CDCl₃) δ : 1.62 - 2.60 (8H, m), 3.60 - 3.
10 98, 4.04 - 4.33 (total 2H, each m), 5.11 -
5.56 (2H, m), 7.00 - 8.02 (8H, m), 8.33 - 8.4
8 (1H, m), 8.57 - 8.71 (1H, m), 10.76 - 11.09
(1H, m)

ESI-MS (m/e) : 459 [M+H]

15

実施例 585

6 - (1 - アセチル - 3 - フルオロピリジン - 2 - イル) - 5 - ((6 - クロ
ロピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイ
ミダゾール

20 6 - クロロピリジン - 3 - オールを用いて、実施例 575 と同様の方法、こ
れに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を
油状物質として得た。

¹H NMR (CDCl₃) δ : 1.54 - 2.45 (5H, m), 3.60 - 4.
35 (2H, m), 5.20 - 5.60 (2H, m), 6.90 - 7.00,
25 7.21 - 7.43, 7.60 - 7.93 (total 6H, each
m), 8.22 - 8.45 (2H, m), 8.58 - 8.70 (1H, m),
10.63 - 10.90 (1H, m)

ESI-MS (m/e) : 452 [M+H]

実施例 586

6 - (1-アセチルピロリジン-2-イル) - 5 - ((6 - (5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-イル)オキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール

- 5 6 - (5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)ピリジン-3-オールを用いて、実施例 570 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。
- ¹H NMR (CDCl₃) δ : 1.60 - 2.47 (7H, m), 2.57 - 2.73 (3H, m), 3.57 - 3.93 (2H, m), 5.21 - 5.48 (1H, m), 7.00 - 7.76 (3H, m), 7.96 - 8.14 (1H, m), 8.52 - 8.68 (3H, m), 9.54 - 9.65 (1H, m), 10.70 - 11.02, 11.53 - 10.66 (total 1H, each m)

ESI-MS (m/e) : 483 [M+H]

15

実施例 587

6 - (1-アセチルピロリジン-2-イル) - 5 - ((6 - (メタンスルホニル)ピリジン-3-イル)オキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール

- 20 6 - (メタンスルホニル)ピリジン-3-オールを用いて、実施例 570 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を油状物質として得た。
- ¹H NMR (CDCl₃) δ : 1.51 - 2.47 (7H, m), 3.14 - 3.27 (3H, m), 3.58 - 3.92 (2H, m), 5.14 - 5.40 (1H, m), 7.03 - 7.79 (4H, m), 7.95 - 8.11 (1H, m), 8.48 - 8.71 (2H, m), 9.56 - 9.66 (1H, m), 10.65 - 10.94, 11.34 - 11.49 (total 1H, each m)

ESI-MS (m/e) : 479 [M+H]

25

実施例 588

1- (4- ((6- (1-アセチルピロリジン-2-イル) -2-ピラジン-
2-イル-1H-ベンズイミダゾール-5-イル) オキシ) フェニル) エタノ
5 ン

1- (4-ヒドロキシフェニル) エタノンを用いて、実施例 570 と同様の
方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題
化合物を油状物質として得た。

¹H NMR (CDCl₃) δ: 1.53-2.61 (10H, m), 3.51-
10 3.93 (2H, m), 5.14-5.47 (1H, m), 6.95-7.7
4 (4H, m), 7.88-8.02 (2H, m), 8.53-8.68 (2
H, m), 9.54-9.66 (1H, m), 10.60-10.88, 11.
43-11.54 (total 1H, each m)

ESI-MS (m/e): 442 [M+H]

15

実施例 589

6- (1-アセチルピロリジン-2-イル) -5- ((6- (ジフルオロメト
キシ) ピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベン
ズイミダゾール

20 6- (ジフルオロメトキシ) ピリジン-3-オールを用いて、実施例 338
(工程 5) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせ
ることにより、表題化合物を淡黄色固体として得た。

¹H NMR (CD₃OD) δ: 1.92 and 2.18 (total 3H,
each s), 1.98-2.57 (4H, m), 3.65-4.00 (2
25 H, m), 5.41-5.48 (1H, m), 7.03 and 7.07
(total 1H, each d, J=8.8 Hz), 7.00-7.72
(5H, m), 7.94-8.00 (1H, m), 8.08 (1H, s), 8.
25 (1H, t, J=7.4 Hz), 8.73 (1H, s)

ESI-MS (m/e): 466 [M+H]

実施例 590

6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 5 -
(4 - ピラジン - 2 - イルフェノキシ) - 1H - ベンズイミダゾール

- 5 4 - ピラジン - 2 - イルフェノールを用いて、実施例 526 と同様の方法、
 これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物
 を白色固体として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10 - 2.60 (7H, m), 3.50 - 4.00 (2H, m), 5.20 - 5.60 (1H, m), 6.70 - 7.80
 10 (4H, m), 7.90 - 8.20 (2H, m), 8.50 - 8.80 (4H, m), 8.95 - 9.20 (1H, m), 9.50 - 9.75 (1H, m),
 10.60 - 11.40 (1H, m)
 ESI-MS (m/e) : 478 [M+H]

15 実施例 591

4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール - 5 - イル) オキシ) ベンゾニトリル

- 20 4 - シアノフェノールを用いて、実施例 526 と同様の方法、これに準じた
 方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物
 質として得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50 - 2.50 (7H, m), 3.50 - 3.90 (2H, m), 5.05 - 5.50 (1H, m), 6.65 - 7.80
 (6H, m), 8.50 - 8.80 (2H, m), 9.50 - 9.70 (1H, m), 10.40 - 11.20 (1H, m)
 25 ESI-MS (m/e) : 425 [M+H]

実施例 592

メチル 4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1H - ベンズイミダゾール - 5 - イル) オキシ) ベンゾエート

メチル4-ヒドロキシベンゾエートを用いて、実施例526と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を黄色油状物質として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.60–2.50 (7H, m), 3.50–4.00 (5H, m), 5.10–5.60 (1H, m), 6.70–7.80 (4H, m), 7.90–8.20 (2H, m), 8.50–8.70 (2H, m), 9.50–9.70 (1H, m), 10.60–11.60 (1H, m)

ESI-MS (m/e): 458 $[\text{M}+\text{H}]$

10

実施例593

2-(5-(2-(2-フルオロビフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-1-カルボキサミド

15 2-(2-フルオロビフェニル-4-イル)を用いて、実施例182と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ : 1.60–2.60 (4H, m), 3.20–4.20 (2H, m), 5.10–5.30 (1H, m), 5.60–5.90 (2H, m), 6.90–7.70 (11H, m), 7.90–8.10 (1H, m), 8.20–8.40 (1H, m), 8.60–8.80 (1H, m)

ESI-MS (m/e): 494 $[\text{M}+\text{H}]$

25 実施例594

6-(1-アセチルピロリジン-2-イル)-5-(4-(5-メチル-[1,2,4]-オキサジアゾール-3-イル)フェノキシ)-2-ピラジン-2-イル-1H-ベンズイミダゾール

4-(5-メチル-[1,2,4]-オキサジアゾール-3-イル)フェ

ノールを用いて、実施例 526 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

^1H NMR (CDCl_3) δ : 1.60–2.80 (10H, m), 3.50–4.00 (2H, m), 5.15–5.60 (1H, m), 6.70–7.80 (5H, m), 7.90–8.20 (2H, m), 8.50–8.70 (1H, m), 9.50–9.70 (1H, m), 10.60–11.50 (1H, m)

ESI-MS (m/e): 482 [M+H]

10 実施例 595

6-((2R, 5S) -1-アセチル-5-メチルピロリジン-2-イル) -5-(4-メタンスルホニル-フェノキシ) -2-ピラジン-2-イル-1H-ベンズイミダゾール

(工程 1)

15 2-フルオロ-N-メトキシ-N-メチルベンズアミドの合成

2-フルオロ-4-ニトロ安息香酸 10 g のピリジン 80 ml 懸濁液に、N-メトキシ-N-メチルアミン塩酸塩 5.79 g 及び 1-エチル-3-(3-ジメチルアミノプロピル)-カルボジイミド塩酸塩 12.4 g を加え、反応液を室温にて一終夜攪拌した。ピリジンを減圧留去した後、水を加えた。得られた沈殿物を濾取し、水で洗浄後、乾燥することにより、表題化合物を淡黄色固体として得た。

(工程 2)

4-アミノ-2-フルオロ-N-メトキシ-N-メチルベンズアミドの合成

2-フルオロ-N-メトキシ-N-メチルベンズアミド 10.84 g のメタノール 60 ml 及び水 30 ml 懸濁液に、塩化アンモニウム 15.2 g 及び鉄粉 8 g を加え、反応液を 3 時間加熱還流した。セライトを用いて反応液を濾去した後、溶媒を減圧留去した。得られた残渣を酢酸エチルにて希釈し、水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル = 9

／1～1／2)にて精製し、表題化合物を褐色油状物質として得た。

(工程3)

N-(3-フルオロ-4-((N-メトキシ-N-メチルアミノ)カルボニル)フェニル)ピラジン-2-カルボキサミドの合成

- 5 4-アミノ-2-フルオロ-N-メトキシ-N-メチルベンズアミド3.7 gのピリジン20 ml溶液に、ピラジン-2-カルボン酸2.56 g及び1-エチル-3-(3'-ジメチルアミノプロピル)-カルボジイミド塩酸塩4.66 gを加え、反応液を室温にて1時間攪拌した。ピリジンを減圧留去した後、残渣を酢酸エチルにて希釈し、水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた固体を酢酸エチル及びヘキサンの混合溶媒で洗淨することにより、表題化合物を淡黄色固体として得た。
- 10

(工程4)

N-(4-((4R)-4-((tert-ブチル(ジメチル)シリル)オキシ)-2-ペンチノイル)-3-フルオロフェニル)ピラジン-2-カルボキサミドの合成

15

- (3R)-3-(tert-ブチル(ジメチル)シリル)オキシ-1-ブチン4.92 gのテトラヒドロフラン80 ml溶液に、-78度にてn-ブチルリチウム(2.46 Mヘキサン溶液)10.8 mlを加え、反応液を同温度にて1時間攪拌した。N-(3-フルオロ-4-((N-メトキシ-N-メチルアミノ)カルボニル)フェニル)ピラジン-2-カルボキサミド2.7 gのテトラヒドロフラン60 ml溶液を-78度にて加え、反応液を室温まで昇温後、2時間攪拌した。反応液に水を加え、酢酸エチルにて抽出し、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=9/1～1/1)にて精製し、表題化合物を黄色固体として得た。
- 20
- 25

(工程5)

N-(4-((4R)-4-((tert-ブチル(ジメチル)シリル)オキシ)-ペンタノイル)-3-フルオロフェニル)ピラジン-2-カルボキサミドの合成

N- (4- ((4R) -4- (tert-ブチル (ジメチル) シリル) オキシ) -2-ペンチノイル) -3-フルオロフェニル) ピラジニン-2-カルボキサミド 513 mg のテトラヒドロフラン 5 ml 及びエタノール 20 ml の混合溶液に、10%パラジウム-炭素触媒 100 mg を加え、反応液を水素雰囲気下、1.5時間攪拌した。触媒を濾去後、溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル= 9/1 ~ 1/1) にて精製し、表題化合物を淡黄色固体として得た。

(工程 6)

N- (4- ((4R) -1, 4-ジヒドロキシペンチル) -3-フルオロフェニル) ピラジニン-2-カルボキサミドの合成

N- (4- ((4R) -4- (tert-ブチル (ジメチル) シリル) オキシ) -ペンタノイル) -3-フルオロフェニル) ピラジニン-2-カルボキサミド 340 mg のメタノール 10 ml 及びテトラヒドロフラン 5 ml の混合溶液に、水素化ホウ素ナトリウム 89 mg を加え、反応液を室温にて 30 分間攪拌した。反応液を減圧留去した後、残渣を酢酸エチルにて希釈し、飽和塩化アンモニウム水溶液にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去することにより、粗生成物を得た。得られた粗生成物のテトラヒドロフラン 6 ml 溶液に、氷冷下、テトラブチルアンモニウムフルオリド (1M テトラヒドロフラン溶液) 1.18 ml を加え、反応液を室温にて 2 時間攪拌した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (展開溶媒: ヘキサン/酢酸エチル= 1/1 ~ 酢酸エチル) にて精製し、表題化合物を淡黄色固体として得た。

(工程 7)

N- (4- ((5S) -1-アセチル-5-メチルピロリジン-2-イル) -3-フルオロフェニル) ピラジニン-2-カルボキサミドの合成

N- (4- ((4R) -1, 4-ジヒドロキシペンチル) -3-フルオロフェニル) ピラジニン-2-カルボキサミド 147 mg のクロロホルム 6 ml 懸濁液に、トリエチルアミン 0.26 ml 及びメタンスルホンクロライド 0.11 ml を加え、反応液を室温にて 2 時間攪拌した。反応液をクロロホルムに

て希釈し、飽和重曹水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去することにより、粗生成物を得た。得られた粗生成物のジメチルホルムアミド 4 ml 溶液に、氷冷下、アジ化ナトリウム 3.0 mg を加え、反応液を室温にて一終夜撹拌した。反応液を酢酸エチルにて希釈し、水及び飽和食塩水
5 にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去することにより、粗生成物を得た。得られた粗生成物のメタノール 5 ml 溶液に、硫酸銅 5 水和物 15 mg 及び水素化ホウ素ナトリウム 52 mg を加え、反応液を室温にて 2 時間撹拌した。水素化ホウ素ナトリウム 35 mg を加え、反応液を 30 分間撹拌した。更に、水素化ホウ素ナトリウム 35 mg を加え、反応液を 30 分
10 間撹拌した。溶媒を減圧留去した後、残渣をクロロホルムにて希釈し、飽和重曹水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去することにより、粗生成物を得た。得られた粗生成物のクロロホルム 4 ml 溶液に無水酢酸 0.043 ml を加え、反応液を室温にて一終夜撹拌した。溶媒を減圧留去した後、分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄、
15 Art 5744 (メルク社製)、酢酸エチル/メタノール=10/1) にて精製し、表題化合物を淡黄色油状物質として得た。

(工程 8)

N-(4-((2R, 5S)-1-アセチル-5-メチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピラジン-2-カルボキサミド
20 の合成

N-(4-((5S)-1-アセチル-5-メチルピロリジン-2-イル)-3-フルオロフェニル)ピラジン-2-カルボキサミド 59 mg に、室温にて発煙硝酸 1 ml を加え、反応液を同温度にて 30 分間撹拌した。反応液をクロロホルムにて希釈し、飽和重曹水にて洗浄後、無水硫酸マグネシウムで
25 乾燥した。溶媒を減圧留去した後、分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄、Art 5744 (メルク社製)、酢酸エチル) にて精製し、表題化合物を淡黄色油状物質として得た。(Rf: トランス体 > シス体)

(工程 9)

6 - ((2R, 5S) - 1 - アセチル - 5 - メチルピロリジン - 2 - イ
 ル) - 5 - (4 - メタンスルホニル - フェノキシ) - 2 - ピラジン - 2 - イ
 ル - 1H - ベンズイミダゾールの製造

N - (4 - ((2R, 5S) - 1 - アセチル - 5 - メチルピロリジン - 2 -
 5 イル) - 5 - フルオロ - 2 - ニトロフェニル) ピラジン - 2 - カルボキサミド
 10 10.4 mg の N - メチルピロリジノン 1 ml 溶液に、4 - メタンスルホニ
 ル - フェノール 9.2 mg、炭酸セシウム 26.2 mg を加え、反応液を 90
 度にて 1 時間攪拌した。塩化スズ (II) 二水和物 60 mg を加え、反応液を
 90 度にて 1 時間、100 度にて 2 時間攪拌した。反応液に酢酸エチル及び飽
 10 和重曹水を加え、沈殿物を濾去後、酢酸エチルにて抽出し、有機層を水及び飽
 和食塩水で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去した後、
 分取用薄層クロマトグラフィー (KieselgelTM 60 F₂₅₄, Art 57
 44 (メルク社製)、クロロホルム/メタノール = 10/1) にて精製し、表
 題化合物を淡黄色油状物質として得た。

15 ¹H NMR (CDCl₃) δ : 1.31 and 1.33 (total 3H,
 each d, J = 6.0 Hz), 1.55 - 2.60 (7H, m), 3.0
 3 - 3.10 (3H, m), 4.25 - 4.62 (1H, m), 5.20 - 5.
 44 (1H, m), 7.01 - 7.68 (4H, m), 7.85 - 7.97
 (2H, m), 8.57 - 8.69 (2H, m), 9.56 - 9.63 (1H,
 20 m)

ESI-MS (m/e) : 492 [M+H]

実施例 596

N - メチル - 2 - (2 - (5 - (4 - (2 - メチル - 2H - テトラゾール -
 25 5 - イル) フェノキシ) - 2 - ピリジン - 2 - イル - 1H - ベンズイミダゾー
ル - 6 - イル) ピロリジン - 1 - イル) - 2 - オキソエタンアミン

2 - メチル - 2H - テトラゾール - 5 - イルフェノールを用いて、実施例 4
 98 (工程 5) から (工程 8) と同様の方法、これに準じた方法又はこれらと
 常法とを組み合わせることにより、表題化合物を黄色油状物として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.80–2.50 (7H, m), 2.90–4.00 (4H, m), 4.30–4.50 (3H, m), 5.10–5.65 (1H, m), 7.10 (2H, m), 7.20–7.85 (3H, m), 7.80–7.95 (1H, m), 8.05–8.20 (2H, m), 8.30–8.50 (1H, m), 8.50–8.70 (1H, m)
 ESI-MS (m/e): 510 [M+H]

実施例 597

6-(1-アセチルピロリジン-2-イル)-5-((4'-フルオロフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

4'-フルオロフェニル-4-オールを用いて、実施例 483 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.66–2.43 (7H, m), 3.44–3.92 (2H, m), 5.21–5.60 (1H, m), 6.80–7.67 (11H, m), 7.77–7.91 (1H, m), 8.30–8.43 (1H, m), 8.53–8.67 (1H, m), 10.89–11.43 (1H, m)
 ESI-MS (m/e): 493 [M+H]

実施例 598

6-(1-アセチルピロリジン-2-イル)-5-((3'-フルオロフェニル-4-イル)オキシ)-2-ピリジン-2-イル-1H-ベンズイミダゾール

3'-フルオロフェニル-4-オールを用いて、実施例 483 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 1.67–2.44 (7H, m), 3.44–3.

9.2 (2H, m), 5.22-5.58 (1H, m), 6.92-7.68 (1H, m), 7.78-7.93 (1H, m), 8.33-8.45 (1H, m), 8.56-8.68 (1H, m), 10.88-11.38 (1H, m)

5 ESI-MS (m/e) : 493 [M+H]

実施例 599

2-(5-(6-シアノピリジン-3-イル)オキシ)-2-ピリジン-
2-イル-1H-ベンズイミダゾール-6-イル)ピロリジン-1-カルボキ

10 サミド

6-シアノピリジン-3-オールを用いて、実施例 162 及び実施例 182 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を白色固体として得た。

¹HNMR (CD₃OD) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 3.40-3.60 (1H, m), 3.70-3.80 (1H, m), 4.80-5.30 (1H, m), 6.60-6.75 (2H, m), 7.20-7.70 (3H, m), 7.80-8.20 (3H, m), 8.20-8.30 (1H, m), 8.50-8.65 (1H, m), 8.70-8.80 (1H, m)

20 ESI-MS (m/e) : 426 [M+H]

実施例 600

6-(2R, 5S)-1-アセチル-5-メチルピロリジン-2-イル)-
5-(6-(5-メチル-[1, 2, 4]-オキサジアゾール-3-イル)
 25 ピリジン-3-イル)オキシ)-2-ピラジン-2-イル-1H-ベンズイミ
ダゾール

実施例 595 (工程 8) で得られた N-(4-(2R, 5S)-1-アセチル-5-メチルピロリジン-2-イル)-5-フルオロ-2-ニトロフェニル)ピラジン-2-カルボキサミド、及び 4-(5-メチル-[1, 2,

4] -オキサジアゾール-3-イル) フェノールを用いて、実施例595(工程9)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- ¹HNMR (CDCl₃) δ: 1.33 and 1.34 (total 3H, each d, J=6.0 Hz), 1.55-2.60 (7H, m), 2.68 and 2.70 (total 3H, each s), 4.26-4.62 (1H, m), 5.28-5.49 (1H, m), 7.03-8.12 (4H, m), 8.40-8.69 (3H, m), 9.57-9.63 (1H, m)
- ESI-MS (m/e): 497 [M+H]

実施例601

- 6-(1-アセチルピロリジン-2-イル)-2-(5-メチルピラジン-2-イル)-5-(4-(2-メチル-2H-テトラゾール-5-イル)-フェノキシ)-1H-ベンズイミダゾール

4-(2-メチル-2H-テトラゾール-5-イル) フェノール、及び5-メチルピラジン-2-カルボン酸を用いて、実施例306同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色固体として得た。

- ¹HNMR (CD₃OD) δ: 1.88-2.48 (7H, m), 2.63 and 2.64 (total 3H, each s), 3.61-3.99 (2H, m), 4.41 and 4.42 (total 3H, each s), 5.37-5.4 (1H, m), 7.15-7.55 (2H, m), 7.17 (2H, d, J=8.8 Hz), 8.08 and 8.11 (total 2H, each d, J=8.8 Hz), 8.64 (1H, s), 9.27 and 9.29 (total 1H, each s)
- ESI-MS (m/e): 496 [M+H]

実施例602

6-(1-アセチル-4-メチルピロリジン-2-イル)-5-(4-(メ
ンスルホニル)フェノキシ)-2-ピリジン-2-イル-1H-ベンズイミダ
ゾール

(工程1)

- 5 N-(3-フルオロ-4-(3-メチル-3-ブテノイル)フェニル)ピリジン-2-カルボキサミドの合成

ピリジン-2-カルボン酸を用いて、実施例145(工程3)と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより得られたN-(3-フルオロ-4-(メトキシ(メチル)アミノ)カルボニル)フェニル)
10)ピリジン-2-カルボキサミド500mgのテトラヒドロフラン10ml溶液に、氷冷下、塩化(2-メチル-2-プロペン-1-イル)マグネシウム(0.50M テトラヒドロフラン溶液)9.89mlを加えた。反応液を氷冷下にて3時間攪拌した後、反応液を水に注ぎ、酢酸エチルにて抽出、無水硫酸ナトリウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラム
15 クロマトグラフィー(展開溶媒:ヘキサン/酢酸エチル=3/1)にて精製し、表題化合物を得た。

(工程2)

N-(3-フルオロ-4-(1-ヒドロキシ-3-メチル-3-ブテン-1-イル)フェニル)ピリジン-2-カルボキサミドの合成

- 20 N-(3-フルオロ-4-(3-メチル-3-ブテノイル)フェニル)ピリジン-2-カルボキサミド280mgのメタノール5ml溶液に、水素化ホウ素ナトリウム88.8mgを加えた。反応液を室温にて3時間攪拌した後、飽和塩化アンモニウム水溶液に注ぎ、酢酸エチルにて抽出、無水硫酸ナトリウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマト
25 グラフィー(展開溶媒:ヘキサン/酢酸エチル=2/1)にて精製し、表題化合物を得た。

(工程3)

N-(4-(1,4-ジヒドロキシ-3-メチルブチル)-3-フルオロフェニル)ピリジン-2-カルボキサミドの合成

シクロヘキセン0.082mlのテトラヒドロフラン5ml溶液に、氷冷下、
ボラン-メチルスルフィド錯体(1M ジクロロメタン溶液) 1.20mlを
加えた。反応液を氷冷下10分間攪拌した後、N-(3-フルオロ-4-(1-
-ヒドロキシ-3-メチル-3-ブテン-1-イル)フェニル)ピリジン-2
5 -カルボキサミド301mgのテトラヒドロフラン3ml溶液を加え、反応液
を室温にて1時間攪拌した。反応液に5規定水酸化ナトリウム水溶液及び35
%過酸化水素水溶液0.50mlを順次加え、室温で10分間攪拌した。反応
液を飽和塩化アンモニウム水溶液に注ぎ、酢酸エチルにて抽出、無水硫酸ナト
リウムにて乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムク
10 ロマトグラフィー(展開溶媒:クロロホルム/メタノール=9/1)にて精製
し、表題化合物を得た。

(工程4)

N-(3-フルオロ-4-(4-メチルピロリジン-2-イル)フェニル)ピ
リジン-2-カルボキサミドの合成

15 N-(4-(1,4-ジヒドロキシ-3-メチルブチル)-3-フルオロフェ
ニル)ピリジン-2-カルボキサミド236mgのクロロホルム5ml溶液
に、氷冷下、トリエチルアミン0.62ml及び塩化メタンスルホニル0.2
3mlを順次加え、反応液を室温にて3時間攪拌した。反応液を飽和重曹水に
注ぎ、クロロホルムにて抽出した後、無水硫酸ナトリウムにて乾燥した。溶媒
20 を減圧留去し、粗生成物を得た。得られた粗生成物のジメチルホルムアミド3
ml溶液に、氷冷下、アジ化ナトリウム53.0mgを加えた。反応液を氷冷
下にて30分間攪拌した後、室温にて3時間攪拌した。反応液を酢酸エチルに
て希釈し、水にて洗浄後、無水硫酸ナトリウムにて乾燥した。溶媒を減圧留去
し、粗生成物を得た。得られた粗生成物のメタノール4ml溶液に、硫酸銅5
25 水和物20mg及び水素化ホウ素ナトリウム168mgを順次加えた。反応液
を室温にて4時間攪拌した後、飽和重曹水に注ぎ、クロロホルムにて抽出、無
水硫酸ナトリウムにて乾燥した。溶媒を減圧留去し、粗生成物を得た。得られ
た粗生成物のクロロホルム3ml溶液に、無水酢酸0.050mlを加え、反
応液を室温にて30分間攪拌した。溶媒を減圧留去し、残渣をシリカゲルカラ

ムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／3）にて精製し、表題化合物を得た。

（工程5）

5 N-（4-（1-アセチル-4-メチルピロリジン-2-イル）-5-フルオロ-2-ニトロフェニル）ピリジン-2-カルボキサミドの合成

N-（3-フルオロ-4-（4-メチルピロリジン-2-イル）フェニル）ピリジン-2-カルボキサミド 70.7 mg を発煙硝酸 1 ml に溶解し、反応液を室温にて 10 分間攪拌した。反応液を飽和重曹水に注ぎ、酢酸エチルにて抽出、無水硫酸ナトリウムにて乾燥した。溶媒を減圧留去し、得られた残渣を
10 シリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／2）にて精製し、表題化合物を得た。

（工程6）

6-（1-アセチル-4-メチルピロリジン-2-イル）-5-（4-（メタンスルホニル）フェノキシ）-2-ピリジン-2-イル-1H-ベンズイミダ
15 ゴールの製造

N-（4-（1-アセチル-4-メチルピロリジン-2-イル）-5-フルオロ-2-ニトロフェニル）ピリジン-2-カルボキサミド 15 mg の N-メチル-ピロリジノン 2 ml 溶液に、4-（メタンスルホニル）フェノール 13.4 mg 及び炭酸セシウム 44.9 mg を順次加え、反応液を 90 度にて 1 時間
20 攪拌した。反応液に塩化スズ 2 水和物 43.8 mg を加えたのち、100 度に昇温して 2 時間攪拌した。反応液を酢酸エチルに溶解した後、飽和重曹水にて洗浄、無水硫酸ナトリウムにて乾燥した。溶媒を減圧留去し、得られた残渣を分取用薄層クロマトグラフィー（Kieselgel TM 60 F 254、Art 5744（メルク社製）、クロロホルム／メタノール＝9／1）にて精製し、
25 表題化合物を白色固体として得た。

$^1\text{H NMR}$ (CDCl_3) δ : 0.80–2.63 (9H, m), 3.00–4.40 (2H, m), 3.05 and 3.08 (total 3H, each s), 5.03–5.43 (1H, m), 7.00–7.73 (5H, m), 7.83–7.98 (3H, m), 8.33–8.43 (1H, m), 8.62–

8. 70 (1H, m), 10. 62-10. 80 (1H, m)

ESI-MS (m/e) : 491 [M+H]

実施例 603

5 6-((2R, 5S)-1-アセチル-5-メチルピロリジン-2-イル) -
5-((6-(メトキシメチル) ピリジン-3-イル) オキシ) -2-ピラジ
ン-2-イル-1H-ベンズイミダゾール

実施例 595 (工程 8) で得られた N-(4-((2R, 5S)-1-アセチル-5-メチルピロリジン-2-イル) -5-フルオロ-2-ニトロフェニ
 10 ル) ピラジン-2-カルボキサミド、及び 6-(メトキシメチル) ピリジン-3-オールを用いて、実施例 595 (工程 9) と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を淡黄色油状物質として得た。

¹H NMR (CDCl₃) δ : 1. 10-2. 22 (10H, m), 3. 48
 15 and 3. 50 (total 3H, each s), 4. 26-4. 62 (1H, m), 4. 57 and 4. 59 (total 2H, each s), 5. 33-5. 52 (1H, m), 7. 20-7. 50 (4H, m), 8. 40-8. 70 (3H, m), 9. 57-9. 63 (1H, m)

ESI-MS (m/e) : 459 [M+H]

20 参考例 1

[1, 2, 4] チアジアゾール-5-カルボン酸

チオオキサム酸エチル 1 g のクロロホルム 10 ml 溶液に、N, N-ジメチルホルムアミドジメチルアセタール 2 ml を加え、反応液を室温にて 4 時間攪拌した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラ
 25 フィー (展開溶媒 : ヘキサン/酢酸エチル = 9/1 ~ 1/2) にて精製し、アミジン体 1. 1 g を赤色油状物質として得た。

アミジン体 1. 09 g 及びピリジン 0. 95 ml のエタノール 18 ml 溶液に、ヒドロキシルアミン-O-スルホン酸 721 mg のエタノール 20 ml 溶液を加え、反応液を室温にて終夜攪拌した。溶媒を減圧留去した後、残渣を酢酸エ

チルにて希釈し、飽和重曹水で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝9／1）にて精製し、[1, 2, 4]チアジアゾール-5-カルボン酸エチルエステルを淡黄色油状物質として得た。得られた[1, 2, 4]チアジアゾール-5-カルボン酸エチルエステル300mgのメタノール8ml溶液に、1規定水酸化ナトリウム水溶液5.7mlを加え、反応液を室温にて終夜攪拌した。反応液を減圧留去した後、残渣を2規定塩酸にて中和した。反応液を減圧留去した後、残渣をクロロホルム-メタノール＝10／1にて洗浄し、得られた有機層を減圧留去することにより、表題化合物を白色固体として得た。

参考例2

2-ジフルオロメトキシ-ピリジン-3-オール

3-ベンジルオキシ-2-ヒドロキシピリジン2gのアセトニトリル40ml懸濁液に、炭酸ナトリウム2.1g及びジフルオロフルオロスルホン酢酸1.24mlを加え、反応液を室温にて1時間攪拌した後、溶媒を減圧留去した。残渣を酢酸エチルにて希釈し、水にて洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝9／1～4／1）にて精製し、ジフルオロメトキシ体を淡黄色油状物質として得た。ジフルオロメトキシ体2.38gのメタノール25ml溶液に、10%パラジウム-炭素触媒500mgを加え、反応液を水素雰囲気下室温にて1時間攪拌した。触媒をセライトにより濾去後、溶媒を減圧留去することにより、表題化合物を淡紫色油状物質として得た。

25

参考例3

6-メタンスルホン-ピリジン-3-オール

3-ブロモ-6-メタンスルホン-ピリジン4.72gのジメチルスルホキシド80ml溶液に、ピス（ピナコレート）ジボロン6.6g、酢酸カリウ

- ム 5. 9 g 及び (1, 1'-ビス(ジフェニルホスフィノ)フェロセン) ジクロロパラジウム (II) ジクロロメタン錯体 980 mg を加え、反応液を 80 度にて 2 時間攪拌した。反応液に酢酸エチルと水を加え、不溶物をセライトにより濾去後、有機層を分離した。有機層を水及び飽和食塩水にて洗浄後、無水硫酸マグネシウムで乾燥し、溶媒を減圧留去した。得られた残渣のテトラヒドロフラン 200 ml 溶液に、5 規定水酸化ナトリウム水溶液 60 ml 及び 30% 過酸化水素水 30 ml を 0 度にて加え、反応液を室温にて終夜攪拌した。反応液をジエチルエーテルで希釈後、水にて洗浄した。水層を 5 規定塩酸にて酸性にし、酢酸エチルで抽出した。有機層を無水硫酸マグネシウムで乾燥し、溶媒を減圧留去した。得られた残渣をクロロホルム及びヘキサンの混合溶媒にて洗浄することにより、表題化合物を褐色固体として得た。

参考例 4

6-エタンスルホニル-ピリジン-3-オール

- 15 3-クロロ-6-エタンスルホニル-ピリジンを用いて、参考例 3 と同様の方法、これに準じた方法又はこれらと常法とを組み合わせることにより、表題化合物を得た。

参考例 5

- 20 (2R, 4R)-4-ヒドロキシ-ピロリジン-2-カルボン酸 メトキシ-メチルアミド

(工程 1)

(2R, 4R)-4-(tert-ブチルジフェニルシラニルオキシ)-ピロリジン-1, 2-ジカルボン酸 1-ベンジルエステルの合成

- 25 (2R, 4R)-4-ヒドロキシ-ピロリジン-1, 2-ジカルボン酸 1-ベンジルエステル 3.61 g のジメチルホルムアミド 60 ml 溶液に、塩化 tert-ブチルジフェニルシリル 2.32 g 及びイミダゾール 2.32 g を順次加え、反応液を室温にて一終夜攪拌した。反応液を、酢酸エチルにて希釈し、飽和塩化アンモニウム水溶液、飽和食塩水にて順次洗浄後、無水硫酸ナト

リウムで乾燥した。溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／2）にて精製し表題化合物を得た。

（工程2）

- 5 (2 R, 4 R) - 4 - (tert-ブチル-ジフェニル-シラニルオキシ) - 2 - (メトキシ-メチル-カルバモイル) - ピロリジン-1-カルボン酸 ベンジルエステルの合成

- 10 （工程1）で得られた (2 R, 4 R) - 4 - (tert-ブチル-ジフェニル-シラニルオキシ) - ピロリジン-1, 2-ジカルボン酸 1-ベンジルエステル 2. 62 g のピロリジン 30 ml 溶液に、1 - (3-ジメチルアミノプロピル) - 3-エチルカルボジイミド塩酸塩 1. 50 g 及び O, N-ジメチルヒドロキシルアミン 塩酸塩 761 mg を順次加え、反応液を室温にて一終夜攪拌した。反応液の溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／1）にて精製し表題化合物を得た。
- 15

（工程3）

(2 R, 4 R) - 4 - ヒドロキシ-2-メトキシ-メチル-カルバモイル-ピロリジン-1-カルボン酸 ベンジルエステルの合成

- 20 （工程2）で得られた (2 R, 4 R) - 4 - (tert-ブチル-ジフェニル-シラニルオキシ) - 2 - (メトキシ-メチル-カルバモイル) - ピロリジン-1-カルボン酸 ベンジルエステル 2. 04 g のテトラヒドロフラン 30 ml 溶液に、テトラブチルアンモニウムフルオリド（1M テトラヒドロフラン溶液）7. 46 ml を加え、反応液を室温にて20分間攪拌した。反応液の溶媒を減圧留去し、得られた残渣をシリカゲルカラムクロマトグラフィー（展開溶媒：ヘキサン／酢酸エチル＝1／3）にて精製し表題化合物を得た。
- 25

（工程4）

(2 R, 4 R) - 4 - ヒドロキシ-ピロリジン-2-カルボン酸 メトキシ-メチルアミドの製造

（工程3）で得られた (2 R, 4 R) - 4 - ヒドロキシ-2-メトキシ-メ

チルーカルバモイルーピロリジンー１ーカルボン酸・ベンジルエステル 600 mg のエタノール 20 ml 溶液に、10%パラジウムー炭素触媒 100 mg を加え、反応液を水素雰囲気下、一終夜攪拌した。触媒をセライトにて濾去後、溶媒を減圧留去し、表題化合物を得た。

5

産業上の利用可能性

前記式（I-0）で表される本発明に係る置換ベンズイミダゾール誘導体は優れたグルコキナーゼ活性を示すことから、医薬の分野において糖尿病、糖尿病の合併症若しくは肥満の治療及び／又は予防に有用である。

10

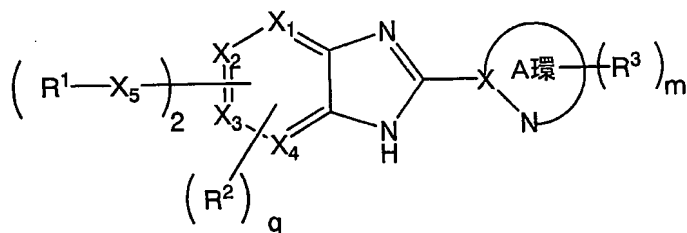
15

20

25

請求の範囲

1. 式 (I-0)

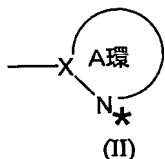


(I-0)

[式中、Xは、炭素原子又は窒素原子を示し、

- 5 X₁、X₂、X₃及びX₄は、それぞれ独立して、炭素原子又は窒素原子を示し、
A環は、式 (I I)

【化1】



- 10 で表される窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ
原子を環内に1乃至3有していてもよい（式 I I 中のN*で表される窒素原子
は除く）5乃至6員の含窒素芳香族複素環を示すか、或いは、該含窒素芳香族
複素環とフェニル又はピリジルとが縮合した双環を示し、

- R¹は、アリールを示すか、或いは、窒素原子、硫黄原子及び酸素原子からなる
群より選択されるヘテロ原子を環内に1乃至4有する4乃至10員の単環の若
しくは双環の複素環を示し（該R¹は、それぞれ独立して、1乃至3のR⁴で置
換されていてもよく、また、該複素環が、脂肪族複素環である場合には、二重
結合を1又は2有していてもよい）、

- 15 R²は、それぞれ独立して、ヒドロキシ、ホルミル、-CH_{3-a}F_a、-OCH_{3-a}F_a、アミノ、CN、ハロゲン、C₁₋₆アルキル又は-(CH₂)₁₋₄OHを
20 示し、

R³は、-C₁₋₆アルキル、-(CH₂)₁₋₆-OH、-C(O)-OC₁₋₆アル
キル、-(CH₂)₁₋₆-OC₁₋₆アルキル、-(CH₂)₁₋₆-NH₂、シア

- ノ、 $-C(O)-C_{1-6}$ アルキル、ハロゲン、 $-C_{2-6}$ アルケニル、 $-OC_{1-6}$ アルキル、 $-COOH$ 、 $-OH$ 又はオキソを示し、
- R^4 は、それぞれ独立して、
- $-C_{1-6}$ アルキル（該アルキルは、同一又は異なる、1乃至3のヒドロキシ、ハ
- 5 ロゲン、 $-OC(O)-C_{1-6}$ アルキル（該アルキルは1乃至3のハロゲンで置換されていてよい）又は $-OC_{1-6}$ アルキルで置換されていてよい）、
- $-C_{3-7}$ シクロアルキル、
- $-C_{2-6}$ アルケニル、
- $-C(O)-N(R^{51})R^{52}$ 、
- 10 $-S(O)_2-N(R^{51})R^{52}$ 、
- $-O-C_{1-6}$ アルキル（該 C_{1-6} アルキルは、ハロゲン又は $N(R^{51})R^{52}$ で置換されていてよい）、
- $-S(O)_{0-2}-C_{1-6}$ アルキル、
- $-C(O)-C_{1-6}$ アルキル（該 C_{1-6} アルキルは、ハロゲン、アミノ、CN、
- 15 ヒドロキシ、 $-O-C_{1-6}$ アルキル、 $-CH_{3-a}F_a$ 、 $-OC(O)-C_{1-6}$ アルキル、 $-N(C_{1-6}アルキル)C(O)O-C_{1-6}$ アルキル、 $-NH-C(O)O-C_{1-6}$ アルキル、フェニル、 $-N(R^{51})R^{52}$ 、 $-NH-C(O)-C_{1-6}$ アルキル、 $-N(C_{1-6}アルキル)-C(O)-C_{1-6}$ アルキル又は $-NH-S(O)_{0-2}-C_{1-6}$ アルキルで置換されていてよい）、
- 20 $-C(S)-C_{3-7}$ シクロアルキル、
- $-C(S)-C_{1-6}$ アルキル、
- $-C(O)-O-C_{1-6}$ アルキル、
- $-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$ 、
- $-N(R^{53})-C(O)-O-R^{54}$ 、
- 25 $-C(O)-アリール$ （該アリールは、ハロゲンで置換されていてよい）、
- $-C(O)-芳香族複素環$ 、
- $-C(O)-脂肪族複素環$ 、
- 複素環（該複素環は、 $-C_{1-6}$ アルキル（該 $-C_{1-6}$ アルキルは、ハロゲン又は $-O-C_{1-6}$ アルキルで置換されていてよい））、

フェニル（該フェニルは、ハロゲン、 $-C_{1-6}$ アルキル、 $-O-C_{1-6}$ アルキルで置換されていてもよい）、

ハロゲン、CN、ホルミル、COOH、アミノ、オキソ、ヒドロキシ、ヒドロキシアミジノ又はニトロを示し、

- 5 R^{51} 及び R^{52} は、それぞれ独立して、水素原子、 $-C_{1-6}$ アルキルを示すか、或いは、窒素原子、 R^{51} 及び R^{52} が一緒になって形成する4乃至7員の複素環を示し、

R^{53} は、水素原子又は $-C_{1-6}$ アルキルを示し、

R^{54} は、 $-C_{1-6}$ アルキルを示すか、或いは、

- 10 R^{53} 及び R^{54} のアルキルと $-N-C(O)-$ とが一緒になって形成する4乃至7員の含窒素脂肪族複素環又は

R^{53} 及び R^{54} のアルキルと $-N-C(O)-O-$ とが一緒になって形成する4乃至7員の含窒素脂肪族複素環（該脂肪族複素環は、オキソで置換されていてもよく、また、該脂肪族複素環は、環内に二重結合を1又は2有していてもよ

- 15 い）を示し、

X_5 は、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 、単結合又は $-O-C_{1-6}$ アルキルを示し、

a は、それぞれ独立して、1、2又は3の整数を示し、

q は、0乃至2の整数を示し、

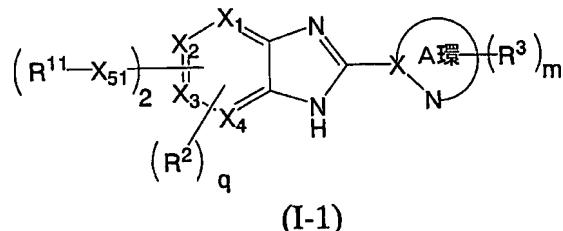
- 20 m は、0乃至2の整数を示す。] で表される化合物（ただし、 X_5 の一方が $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ であり、 X_5 の他方が単結合であって、かつ、 R^1 がアリール又は窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する含窒素芳香族複素環（該アリール又は1乃至3の R^4 で置換されていてもよい）である場合、 X_5 が共に単結合である場合、或いは、 R^1 が共に脂肪族複素環である場合を除く）又はその薬学的に許容される塩。

2. X_1 乃至 X_4 が全て炭素原子である請求項1記載の化合物又はその薬学的に許容される塩。

3. X_5 が、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 又は単結合である

請求項1記載の化合物又はその薬学的に許容される塩。

4. 式 (I-1)



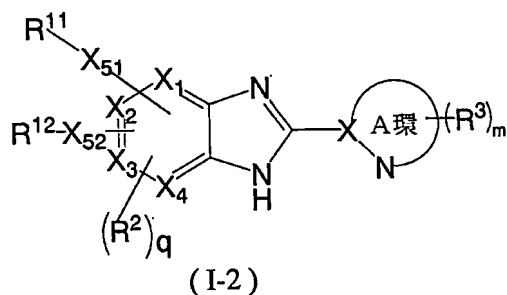
(I-1)

- 5 [式中、 R^{11} は、1乃至3の R^4 で置換されていてもよいフェニルであるか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）を示し、かつ、 X_{51} が $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ を示し、他の記号は前記に同じ]である請求項1記載の化合物又はその薬学的に許容される塩。

5. R^{11} が共に、1乃至3の R^4 で置換されていてもよいフェニルである請求項4記載の化合物又はその薬学的に許容される塩。
6. R^{11} が共に、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）である請求項4記載の化合物又はその薬学的に許容される塩。

7. R^{11} の一方が、1乃至3の R^4 で置換されていてもよいフェニルであり、かつ、 R^{11} の他方が、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3の R^4 で置換されていてもよい）である請求項4記載の化合物又はその薬学的に許容される塩。

8. 式 (I-2)



[式中、

R¹¹は、1乃至3のR⁴で置換されていてもよいフェニルであるか、或いは、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有する5又は6員の含窒素芳香族複素環（該含窒素芳香族複素環は、1乃至3のR⁴で置換されていてもよい）を示し、

10 R^{12} は、複素環を構成するヘテロ原子として、少なくとも窒素原子を1つ有し、かつ、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至4有していてもよい4乃至7員の含窒素複素環（該 R^{12} は、1乃至3の R^4 で置換されていてもよく、また、該複素環が、脂肪族複素環である場合には、二重結合を1又は2有していてもよい）であり、

X_{51} が $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S(O)_2-$ であり、

X₅₂が-O-、-S-、-S(O)-、-S(O)₂-又は単結合であり、他の記号は前記に同じ]である請求項1記載の化合物又はその薬学的に許容される

15 盐。

9. R^{12} が、複素環を構成するヘテロ原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよい4乃至7員の飽和の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1乃至3の R^4 で置換されていてよい）であり、かつ、 X_{52} が単結合であるか、或いは、 R^{12} が、複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環（該5乃至7員の複素環は、1乃至3の前記 R^4 で置換されていてよい）であり、かつ、 X_{52} が、 $-O-$ 、 $-S-$ 、 $-S(O)-$ 又は $-S$

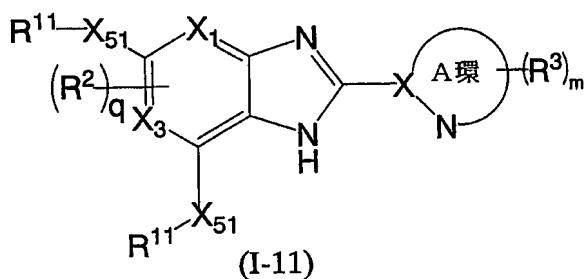
(O)₂である請求項8記載の化合物又はその薬学的に許容される塩。

10. R¹²が、複素環を構成するヘテロ原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよい4乃至7員の飽和の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1乃至3のR⁴で置換されていてよい）であり、かつ、X₅₂が単結合である請求項8記載の化合物又はその薬学的に許容される塩。

11. R¹²が、複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環（該5乃至7員の複素環は、1乃至3の前記R⁴で置換されていていてもよい）であり、かつ、X₅₂が、-O-、-S-、-S(O)-又は-S(O)₂-である請求項8記載の化合物又はその薬学的に許容される塩。

12. R¹²が、複素環を構成する原子として、少なくとも窒素原子を1つ有し、他のヘテロ原子として、窒素原子、硫黄原子及び酸素原子からなる群より選択されるヘテロ原子を1乃至2有していてもよく、また、環内に二重結合を1又は2有する5乃至7員の含窒素脂肪族複素環（該含窒素脂肪族複素環は、1乃至3の前記R⁴で置換されていていてもよい）であり、かつ、X₅₂が、-O-である請求項8記載の化合物又はその薬学的に許容される塩。

13. 式(I-1)が、式(I-11)

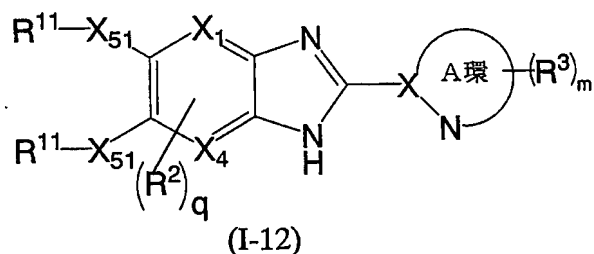


〔式中、各記号は前記に同じ〕である請求項3記載の化合物又はその薬学的に許容される塩。

14. X₅₁が、共に-O-である請求項13記載の化合物又はその薬学的に許

容される塩。

15. 式 (I-1) が、式 (I-12)

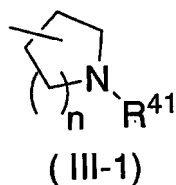


[式中、各記号は前記に同じ] である請求項3記載の化合物又はその薬学的に

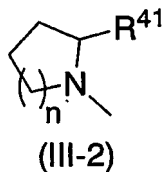
5 許容される塩。

16. X_{51} が、共に-O-である請求項15記載の化合物又はその薬学的に許容される塩。

17. R^{12} が、式 (III-1)



10 又は式 (III-2)



[式中、nは、1乃至3の整数を示し、 R^{41} は、前記 R^4 と同じ] である請求項10記載の化合物又はその薬学的に許容される塩。

18. A環が1乃至3の R^4 で置換されていてもよい、チアゾリル、イミダゾリル、イソチアゾリル、チアジアゾリル、オキサジアゾリル、トリアゾリル、オキサゾリル、イソキサゾリル、ピラジニル、ピリジル、ピリダジニル、ピラゾリル又はピリミジニルである請求項1乃至17のいずれか1項に記載の化合物又はその薬学的に許容される塩。

19. 式 (I-0) で表される化合物が、5-(4-メタンスルホニルフェノキシ)-2-ピラジン-2-イル-6-(2-カルバモイルフェノキシ)

- ー1H-ベンズイミダゾール、
5-（2-カルバモイル-フェノキシ）-2-ピリジン-2-イル-6-（6-メタンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール、
- 5 5-（2-カルバモイル-フェノキシ）-2-ピラジン-2-イル-6-（6-メタンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール、
5-（2-フルオロ-フェノキシ）-2-ピリジン-2-イル-6-（6-メタンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール、
- 10 5-（2-ジフルオロメトキシ-ピリジン-3-イルオキシ）-6-（6-メタンスルホニル-ピリジン-3-イルオキシ）-2-ピリジン-2-イル-1H-ベンズイミダゾール、
5-（2-ジフルオロメトキシ-ピリジン-3-イルオキシ）-6-（6-メタンスルホニル-ピリジン-3-イルオキシ）-2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 15 5-（2-ジフルオロメトキシ-ピリジン-3-イルオキシ）-6-（6-メタンスルホニル-ピリジン-3-イルオキシ）-2-（1-メチル-1H-ピラゾール-3-イル）-1H-ベンズイミダゾール、
5-（2-シアノ-フェノキシ）-2-ピリジン-2-イル-6-（6-エタンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール、
- 20 5-（2-フルオロ-フェノキシ）-2-ピリジン-2-イル-6-（6-エタンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール、
5-（2-フルオロ-フェノキシ）-2-（1H-ピラゾール-3-イル）-6-（6-エタンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール、
- 25 5-（2, 3-ジフルオロ-フェノキシ）-2-（1-メチル-1H-ピラゾール-3-イル）-6-（6-エタンスルホニル-ピリジン-3-イルオキシ）-1H-ベンズイミダゾール、

- 5 - (2, 4-ジフルオロ-フェノキシ) - 2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 5 - (2, 5-ジフルオロ-フェノキシ) - 2-ピリジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2, 6-ジフルオロ-フェノキシ) - 2-ピラジン-2-イル-6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 10 5 - (2, 6-ジフルオロ-フェノキシ) - 2-(1-メチル-1H-ピラゾール-3-イル) - 6-(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイミダゾール、
- 5 - (2-フルオロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミ
15 ダゾール、
- 5 - (2-フルオロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 5 - (2-クロロピリジン-3-イルオキシ) - 6-(6-エタンスルホニル
20 ピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 5 - (2-クロロピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダゾール、
- 25 5 - (2-シアノピリジン-3-イルオキシ) - 6-(6-エタンスルホニルピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダゾール、

- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (6-エ
タンスルホニル-ピリジン-3-イルオキシ) - 2-ピリジン-2-イル-1
H-ベンズイミダゾール、
- 5 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (6-エ
タンスルホニル-ピリジン-3-イルオキシ) - 2-ピラジン-2-イル-1
H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (4-エ
タンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1 H-ベンズイミ
ダゾール、
- 10 5 - (2-ジフルオロメトキシ-ピリジン-3-イルオキシ) - 6 - (4-エ
タンスルホニル-フェノキシ) - 2-ピラジン-2-イル-1 H-ベンズイミ
ダゾール、
- 5 - (2, 6-ジフルオロ-フェノキシ) - 2-ピリジン-2-イル-6 -
(6-メタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイミダ
15 ゾール、
- 5 - (2-カルバモイル-フェノキシ) - 2-ピリジン-2-イル-6 -
(6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイミダ
ゾール、
- 5 - (2-フルオロ-6-シアノ-フェノキシ) - 2-ピリジン-2-イル-
20 6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベンズイ
ミダゾール、
- 5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピリジン-2-
イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1 H-ベ
ンズイミダゾール、
- 25 5 - (2-フルオロ-6-カルバモイル-フェノキシ) - 2-ピラジン-2-
イル-6 - (4-エタンスルホニル-フェノキシ) - 1 H-ベンズイミダゾー
ル、

- 5 - (2-フルオロ-6-シアノ-フェノキシ) - 2-ピラジン-2-イル-
6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) - 1H-ベンズイ
ミダゾール、
- 5 - (2-フルオロ-6-(テトラゾール-5-イル)-フェノキシ) - 2-
5 ピラジン-2-イル-6 - (6-エタンスルホニル-ピリジン-3-イルオキ
シ) - 1H-ベンズイミダゾール、
- 5 - (2-ジフルオロメトキシピリジン-3-イルオキシ) - 6 - (3-クロ
ロ-4-メタンスルホニル-フェノキシ) - 2-ピリジン-2-イル-1H-
ベンズイミダゾール、
- 10 4 - (2-フルオロ-フェノキシ) - 2 - (ピリジン-2-イル) - 6 -
(4-メタンスルホニル-フェノキシ) - 1H-ベンズイミダゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-メタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダ
ゾール、
- 15 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-メタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダ
ゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピラジン-2-イル-1H-ベンズイミダ
20 ゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2-ピリジン-2-イル-1H-ベンズイミダ
ゾール、
- 4 - (1-メチル-2-オキソ-1, 2-ジヒドロ-ピリジン-3-イルオキ
25 シ) - 6 - (4-エタンスルホニル-フェノキシ) - 2-ピリジン-2-イ
ル-1H-ベンズイミダゾール、
- 4 - (2, 6-ジフルオロ-フェノキシ) - 6 - (6-エタンスルホニル-ピ
リジン-3-イルオキシ) - 2 - (1H-ピラゾール-3-イル) - 1H-ベ
ンズイミダゾール、

- 4 - (2 - フルオローフェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 4 - (2, 3 - ジフルオローフェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダ
5 ゾール、
- 4 - (2, 5 - ジフルオローフェノキシ) - 6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダ
ゾール、
- 4 - (2 - シアノ - 6 - フルオローフェノキシ) - 6 - (6 - エタンスルホニ
10 ル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイ
ミダゾール
- 4 - (2 - シアノ - 6 - フルオローフェノキシ) - 6 - (6 - メタンスルホニ
ル - ピリジン - 3 - イルオキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイ
ミダゾール、
- 15 4 - (2 - シアノ - 6 - フルオローフェノキシ) - 6 - (6 - メタンスルホニ
ル - ピリジン - 3 - イルオキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイ
ミダゾール、
- 1 - (2 - (6 - (5 - プロモ - ピリジン - 2 - イルオキシ) - 2 - ピリジ
ン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
20 ル) - エタノン、
- 1 - (2 - (6 - (6 - メタンスルホニル - ピリジン - 3 - イルオキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
ン - 1 - イル) - エタノン、
- 1 - (2 - (6 - (4 - ヒドロキシメチル - フェノキシ) - 2 - ピリジン -
25 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - エタノン、
- 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン -
2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - エタノン、

- 2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イ
ル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - カルボキサミ
ド、
- 2 - ヒドロキシ - 1 - (2 - (6 - (4 - メタンスルホニル - 1 - フェノキ
5 シ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピ
ロリジン - 1 - イル) - エタノン、
- 1 - (2 - (6 - (6 - エタンスルホニル - ピリジン - 3 - イルオキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
ン - 1 - イル) - エタノン、
- 10 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピラジン -
2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - エタノン、
- 2 - フルオロ - 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
15 ン - 1 - イル) - エタノン、
- 5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン - 2 - イ
ル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - ピリジン - 2 - カルボニ
トリル、
- 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン -
20 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イ
ル) - 2 - メチルアミノ - エタノン、
- 1 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - (1 H - ピラ
ゾール - 3 - イル) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン -
1 - イル) - エタノン、
- 25 1 - (4 - フルオロ - 2 - (6 - (4 - メタンスルホニル - フェノキシ) -
2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジ
ン - 1 - イル) - エタノン、
- N - (5 - (6 - (1 - アセチル - ピロリジン - 2 - イル) - 2 - ピリジン -
2 - イル - 1 H - ベンズイミダゾール - 5 - イルオキシ) - ピリジン - 2 - イ

- ル) -アセタミド、
 1 - (2 - (2 - (5 - プロモ - ピリジン - 2 - イル) - 6 - (4 - メタンスルホニル - フェノキシ) - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - エタノン、
- 5 N - (2 - (2 - (6 - (4 - メタンスルホニル - フェノキシ) - 2 - ピリジン - 2 - イル - 3 H - ベンズイミダゾール - 5 - イル) - ピロリジン - 1 - イル) - 2 - オキソ - エチル) - アセタミド、
 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (メトキシメチル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール・ートリフルオロ酢酸塩、
- 10 1 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) ピリジン - 2 (1 H) - オン、
 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 15 (2 - (2 - (5 - ((2' - フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 6 - イル) ピロリジン - 1 - イル) - 2 - オキソエチル) メチルアミン、
- 20 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - ([1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピラジン - 2 - イル - 1 H -
- 25 ベンズイミダゾール、
 5 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 6 - (4 - (メタンスルホニル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (2 - メチル - 2

- H-テトラゾール-5-イル) ピリジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、
- 6-(1-アセチルピロリジン-2-イル) -5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ) -2-ピリジン-2-イル-1H-
 5 ベンズイミダゾール、
- 5-(1-アセチル-5-メチルピロリジン-2-イル) -6-(4-(メタン
 スルホニル) フェノキシ) -2-ピリジン-2-イル-1H-ベンズイミダ
 ザール、
- 6-(1-アセチルピロリジン-2-イル) -5-(6-(2-メチル-2
 10 H-テトラゾール-5-イル) ピリジン-3-イル) オキシ) -2-ピラジン
 -2-イル-1H-ベンズイミダゾール、
- 6-(1-アセチルピロリジン-2-イル) -5-(6-(メトキシメチルピ
 リジン-3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダ
 ザール、
- 15 2-(2-(5-(4-(2-メチル-2H-テトラゾール-5-イル) フェ
 ノキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル)
 ピロリジン-1-イル) -2-オキソエタノール、
- 2-(5-(4-(2-メチル-2H-テトラゾール-5-イル) フェノキシ
) -2-ピリジン-2-イル-1H-ベンズイミダゾール-6-イル) ピロリ
 20 ジン-1-カルボキサミド、
- 5'-((6-(1-アセチルピロリジン-2-イル) -2-ピリジン-2-
 イル-1H-ベンズイミダゾール-5-イル) オキシ) -2H-1, 2'-ビ
 ピリジン-2-オン、
- 3-(4-((6-(1-アセチルピロリジン-2-イル) -2-ピリジン-
 25 2-イル-1H-ベンズイミダゾール-5-イル) オキシ) フェニル) -1,
 3-オキサゾリジン-2-オン、
- 6-(1-アセチルピロリジン-2-イル) -5-((6-メチルピリジン-
 3-イル) オキシ) -2-ピリジン-2-イル-1H-ベンズイミダゾール、

- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - ピラジン - 2 - イルピリジン - 3 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 6 - (1 - アセチル - 3 - フルオロピロリジン - 2 - イル) - 5 - ((2' - フルオロビフェニル - 4 - イル) オキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール、
- 3 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) - 1, 3 - オキサゾリジン - 2 - オン、
- 10 6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 5 - ((6 - ピラジン - 2 - イルピリジン - 3 - イル) オキシ) - 1 H - ベンズイミダゾール、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - ((6 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) ピリジン - 3 - イル) オキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 15 1 - (4 - ((6 - (1 - アセチルピロリジン - 2 - イル) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール - 5 - イル) オキシ) フェニル) エタノン、
- 6 - (1 - アセチルピロリジン - 2 - イル) - 5 - (4 - (5 - メチル - [1, 2, 4] - オキサジアゾール - 3 - イル) フェノキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 20 6 - (1 - アセチル - 5 - メチルピロリジン - 2 - イル) - 5 - (4 - メタン sulホニル - フェノキシ) - 2 - ピラジン - 2 - イル - 1 H - ベンズイミダゾール、
- 25 N - メチル - 2 - (2 - (5 - (4 - (2 - メチル - 2 H - テトラゾール - 5 - イル) フェノキシ) - 2 - ピリジン - 2 - イル - 1 H - ベンズイミダゾール - 6 - イル) ピロリジン - 1 - イル) - 2 - オキソエタンアミン、
- 6 - (1 - アセチル - 5 - メチルピロリジン - 2 - イル) - 5 - ((6 - (メトキシメチル) ピリジン - 3 - イル) オキシ) - 2 - ピラジン - 2 - イル - 1

H-ベンズイミダゾール、

1 - (1 - (6 - (4-メタンスルホニル-フェノキシ) - 2-ピリジン-
2-イル-3H-ベンズイミダゾール-5-イル) - ピロリジン-2-イ
ル) - エタノン、

5 1 - (1 - (6 - (6-メタンスルホニル-ピリジン-3-イルオキシ) -
2-ピリジン-2-イル-3H-ベンズイミダゾール-5-イル) - ピロリジ
ン-2-イル) - エタノン、

1 - (1 - (6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) -
2-ピラジン-2-イル-3H-ベンズイミダゾール-5-イル) - ピロリジ
ン-2-イル) - エタノン若しくは

10 1 - (1 - (6 - (6-エタンスルホニル-ピリジン-3-イルオキシ) -
2-ピラジン-2-イル-3H-ベンズイミダゾール-5-イル) - 4-フル
オロ-ピロリジン-2-イル) - エタノンである化合物又はその薬学的に許容
される塩。

15 20. 2型糖尿病の治療、予防及び／又は発症を遅らせるために用いられる以
下の(1) - (3)からなる医薬組成物

(1) 請求項1乃至19のいずれか1項に記載の化合物、

(2) 以下の(a) - (h)からなる群より選択される1又は2以上の化合物

(a) 他のグルコキナーゼ活性化剤

20 (b) ビス-グアニド

(c) PPAR アゴニスト

(d) インスリン

(e) ソマトスタチン

(f) α -グルコシダーゼ 阻害剤

25 (g) インスリン、及び

(h) DPP-IV (ジペプチジルペプチダーゼ IV) 阻害剤

(3) 薬学的に許容される担体。

21. 請求項1乃至19のいずれか1項に記載の化合物又はその薬学的に許容
される塩を有効成分とするグルコキナーゼ活性化剤。

22. 請求項1乃至20のいずれか1項に記載の化合物又はその薬学的に許容される塩を有効成分とする糖尿病の治療及び／又は予防のための薬剤。

23. 請求項1乃至20のいずれか1項に記載の化合物又はその薬学的に許容される塩を有効成分とする肥満の治療及び／又は予防のための薬剤。

5

10

15

20

25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/019843

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl⁷ C07D401/04, 401/12, 401/14, 403/04, 405/14, 413/04, 413/14, 417/04, 417/14, A61K31/4192, 31/4196, 31/4245, 31/426, 31/427, 31/433, 31/4439, 31/444, 31/4709, 31/496, 31/497, 31/506,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl⁷ C07D401/04, 401/12, 401/14, 403/04, 405/14, 413/04, 413/14, 417/04, 417/14, A61K31/4192, 31/4196, 31/4245, 31/426, 31/427, 31/433, 31/4439, 31/444, 31/4709, 31/496, 31/497, 31/506,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 2003/4488 A1 (Kairon Corp.), 16 January, 2003 (16.01.03), Full text & JP 2004-536113 A	1-17, 20-23 18-19
A	JP 2000-26430 A (Taisho Pharmaceutical Co., Ltd.), 25 January, 2000 (25.01.00), Full text (Family: none)	1-23
A	Wolfgang K.-D. Brill, Solid-phase synthesis of 2,6,8-trisubstituted purines, Tetrahedron Letters, 2001, Vol.42, No.37, pages 6515 to 6518	1-23

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
03 March, 2005 (03.03.05)

Date of mailing of the international search report
22 March, 2005 (22.03.05)

Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/019843

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

Int.Cl⁷ 31/5377, A61P3/04, 3/10, 9/10, 13/12, 25/00, 43/00

(According to International Patent Classification (IPC) or to both national classification and IPC)

Continuation of B. FIELDS SEARCHED

Minimum documentation searched (International Patent Classification (IPC))

Int.Cl⁷ 31/5377, A61P3/04, 3/10, 9/10, 13/12, 25/00, 43/00

Minimum documentation searched (classification system followed by classification symbols)

A. 発明の属する分野の分類 (国際特許分類 (IPC)) Int. Cl ⁷ C07D401/04, 401/12, 401/14, 403/04, 405/14, 413/04, 413/14, 417/04, 417/14, A61K31/4192, 31/4196, 31/4245, 31/426, 31/427, 31/433, 31/4439, 31/444, 31/4709, 31/496, 31/497, 31/506, 31/5377, A61P3/04, 3/10, 9/10, 13/12, 25/00, 43/00		
B. 調査を行った分野 調査を行った最小限資料 (国際特許分類 (IPC)) Int. Cl ⁷ C07D401/04, 401/12, 401/14, 403/04, 405/14, 413/04, 413/14, 417/04, 417/14, A61K31/4192, 31/4196, 31/4245, 31/426, 31/427, 31/433, 31/4439, 31/444, 31/4709, 31/496, 31/497, 31/506, 31/5377, A61P3/04, 3/10, 9/10, 13/12, 25/00, 43/00		
最小限資料以外の資料で調査を行った分野に含まれるもの		
国際調査で利用した電子データベース (データベースの名称、調査に使用した用語) CA (STN), REGISTRY (STN)		
C. 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
X A	WO 2003/4488 A1 (カイロン コーポレーション) 2003. 01. 16, 全文 & JP 2004-536113 A	1-17, 20-23 18-19
A	JP 2000-26430 A (大正製薬株式会社) 2000. 01. 25, 全文 (ファミリーなし)	1-23
A	Wolfgang K. -D. Brill, Solid-phase synthesis of 2,6,8-trisubstituted purines, Tetrahedron Letters, 2001, Vol. 42, No. 37, Pages 65 15-6518	1-23
<input type="checkbox"/> C欄の続きにも文献が列挙されている。 <input type="checkbox"/> パテントファミリーに関する別紙を参照。		
* 引用文献のカテゴリー 「A」 特に関連のある文献ではなく、一般的技術水準を示すもの 「E」 国際出願日前の出願または特許であるが、国際出願日後に公表されたもの 「L」 優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す) 「O」 口頭による開示、使用、展示等に言及する文献 「P」 国際出願日前で、かつ優先権の主張の基礎となる出願日の後に公表された文献 「T」 国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの 「X」 特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの 「Y」 特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの 「&」 同一パテントファミリー文献		
国際調査を完了した日 03. 03. 2005		国際調査報告の発送日 22. 3. 2005
国際調査機関の名称及びあて先 日本国特許庁 (ISA/J P) 郵便番号 100-8915 東京都千代田区霞が関三丁目 4番 3号		特許庁審査官 (権限のある職員) 渡辺 仁 4 C 3 2 2 9 電話番号 03-3581-1101 内線 3452